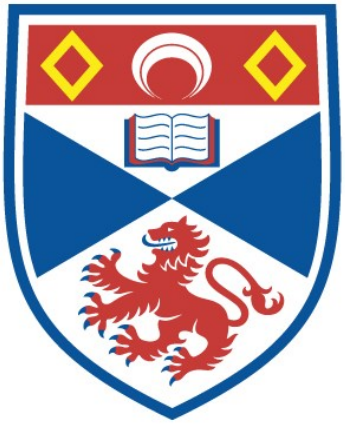
ISOTHIOUREA-MEDIATED SYNTHESIS OF FUNCTIONALISED HETEROCYCLES

Daniel G. Stark

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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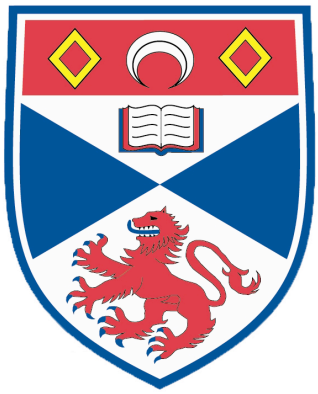

University
of
St Andrews

Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Daniel G. Stark

2016

This thesis is submitted in partial fulfillment for the degree of PhD at the University of St Andrews

Destitutus ventis, remos adhibe

"When the wind will not serve, take to the oars"

- Latin proverb

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Acknowledgements

The challenges faced during the course of a PhD are insurmountable for any one person to confront alone. As such, the work outlined in the thesis is the result of the friendship, mentorship, enthusiasm and positive impact of a number of special people.

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Abstract

The research outlined in this thesis describes methodologies for the synthesis of functionalised heterocycles through the use of C1-ammonium enolate catalysis utilising isothiourea organocatalysts.

Chapter 2: Initial work demonstrated a DHPB-mediated Michael addition-lactamisation/PhSH elimination/*N*- to *O*-sulfonyl transfer one-pot cascade for the synthesis of 2,4,6-substituted pyridine sulfonates. Applying (phenylthio)acetic acid and a range of α,β-unsaturated ketimines, pyridine sulfonates were obtained in moderate to good yield (40-69%) with the functionalisation of the incorporated sulfonate group examined through various derivatisations.

Chapter 3: The established isothiourea-mediated pyridine methodology was expanded into the synthesis of 2,3- and 2,3,5-substituted pyridine 6-tosylates through a three-stage Michael addition-lactamisation, *S*-oxidation-sulfoxide elimination and *N*- to *O*-sulfonyl transfer protocol. Using (phenylthio)acetic acids and 2-*N*-tosyliminoacrylates a range of pyridine products were provided in moderate to good yield over the three-stage process (44-72%). Derivatisation of the installed sulfonate group allowed access into 2,3-, 2,3,5-, 2,3,6 and 2,3,5,6-substituted pyridines.

Chapter 4: Subsequent studies expanded the scope of dihydropyranone and dihydropyridinone products accessible through isothiourea-catalysis using 2-aroyl acrylates or 2-*N*-tosyliminoacrylates in an enantioselective Michael addition-cyclisation process. It was discovered that the use of homoanhydride enolate precursors was necessary when applying 2-aroyl acrylates to ensure high enantioselectivity (up to 99%) and reproducibility of the dihydropyranone products, while carboxylic acids can be used with 2-*N*-tosyliminoacrylates, providing dihydropyridinones in high enantioselectivity (typically >90% ee).

Chapter 5: Enantioselective Michael addition-lactonisation of 2-aryl and 2-alkenylacetic acids and α,β-unsaturated trichloromethyl ketones, catalysed by (2*S*,3*R*)-HyperBTM was shown to give dihydropyranones with subsequent ring opening and substitution of the CCl_3 group providing a range of diesters and diamides in high diastereo- and enantioselectivity (up to 95:5 and up to >99% ee).

Chapter 6: The pyrrolizine core is present in many biologically relevant molecules. It was demonstrated that an isothiourea-catalysed enantioselective Michael addition-lactonisation/ring opening process gives access to these important molecules with exquisite diastereo- and enantioselectivity (typically >95:5 dr and >99% ee). A novel synthetic route into the synthesis of the pyrrole enone-acid substrates was established, hence making the overall methodology more efficient and reproducible. Computational studies are provided to

compliment the synthetic studies with investigations into the origin of the high stereocontrol observed in this process.

Chapter 7: Saccharin-derived Michael acceptors have been shown as useful substrates in isothiourea-catalysis. (2*R*,3*S*)-HyperBTM catalyses the Michael addition-lactamisation of carboxylic acids and saccharin-derived Michael acceptors to give 8,9-dihydro-7*H* benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxides in good to excellent stereocontrol (80:20->95:5 dr and 71->99% ee). Furthermore, these Michael acceptors can be utilised with 1-(1*H*-imidazol-1-yl)-2-(phenylthio)ethan-1-one in a Michael addition-lactamisation/PhSH elimination process giving access to the corresponding 1,2-benzoisothiazolopyridone 1,1-dioxide heterocycle in a chromatography-free procedure.

Publications

The work described in this thesis has formed the basis of the following peer reviewed publications:

"Isothiourea-Mediated One-Pot Synthesis of Functionalized Pyridines"
D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan, A. D. Smith
Angew. Chem. Int. Ed. **2013**, *52*, 11642-11646

"Organocatalytic Michael addition-lactonisation of carboxylic acids using α,β-unsaturated trichloromethyl ketones as α,β-unsaturated ester equivalents"
L.C. Morrill, D. G. Stark, J. E. Taylor, S. R. Smith, J. A. Squires, A. C. A. D'Hollander, C. Simal, P. Shapland, T. J. C. O'Riordan, A. D. Smith
Org. Biomol. Chem. **2013**, *12*, 9016-9027

"Synthesis of Di-, Tri- and Tetrasubstituted Pyridines from (Phenylthio)carboxylic Acids and 2-[Aryl(tosylimino)methyl]acrylates"
D. G. Stark, T. J. C. O'Riordan, A. D. Smith
Org. Lett. **2014**, *16*, 6496-6499

"Enantioselective Synthesis of 3,5,6-Substituted Dihydropyranones and Dihydropyridinones using Isothiourea-Mediated Catalysis"
D. G. Stark, L. C. Morrill, D. B. Cordes, A. M. Z. Slawin, T. J. C. O'Riordan, A. D. Smith
Chem. Asian J. **2016**, *11*, 395-400

"Catalytic Enantioselective Synthesis of Pyrrolizine Carboxylates using Isothiourea Catalysis: A Synthetic and Computational Study"
D. G. Stark, P. Williamson, E. R. Gayner, S. F. Musolino, R. W. F. Kerr, J. E. Taylor, A. M. Z. Slawin, T. J. C. O'Riordan, S. A. Macgregor, A. D. Smith
Org. Biomol. Chem. **2016**, DOI: 10.1039/C6OB01557C

"Enantioselective Isothiourea-Catalysed trans-Dihydropyridinone Synthesis using Saccharin-derived Ketimines: Scope and Limitations"
D. G. Stark, C. M. Young, T. J. C. O'Riordan, A. M. Z. Slawin, A. D. Smith
Org. Biomol. Chem. **2016**, DOI: 10.1039/C6OB01473A

Abbreviations

Ac	Acetyl
APCI	Atmospheric pressure chemical ionisation
aq.	Aqueous
Ar	Aromatic
atm	Atmosphere
ATR	Attenuated total reflectance
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
Bz	Benzoyl
c	Conversion
C	Celsius
CAN	Ceric ammonium nitrate
CI	Chemical ionisation
CMHP	Cumene hydroperoxide
Cy	Cyclohexyl
cm	Centimeter
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexylcarbodiimide
DFT	Density functional theory
DHPB	3,4-Dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole
DIBAL-H	Di-*iso*-butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereoisomeric ratio

EDG	Electron donating group
ee	Enantiomeric excess
eq	Equivalent molar quantity
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IPA	Isopropanol
IR	Infrared
i	Iso
ITU	Isothiourea
J	Coupling constant
LDA	Lithium di-*iso*-propylamide
LiHMDS	Lithium hexamethyldisilazide
LUMO	Lowest occupied molecular orbital
M	Molar (i.e. mol dm^{-3})
MM	Molecular mechanics
mmol	millimole
m	Multiplet
m	*Meta*
Me	Methyl
Mes	Mesityl
MHz	Megahertz
mg	Milligram(s)
mL	Millilitre(s)
mol	Mole(s)
mp	Melting point
M.S.	Molecular sieves
MW	Microwave-assisted reaction
NBS	*N*-Bromosuccinimide

NCS	*N*-Chlorosuccinimide
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Np	Naphthyl
NSI	Nanospray ionisation
Nu	Nucleophile
o	*ortho*
p	*para*
PG	Protecting group
Ph	Phenyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
PS	Polymer supported
py	Pyridine/pyridyl
q	Quartet
quant.	Quantitative
quint	Quintuplet
UV	Ultraviolet
rt	Ambient (room) temperature
s	Singlet
sat.	Saturated
t	Triplet/time
t	*Tert*
T	Temperature
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TS	Transition state
Ts	Tosyl

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Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 1: Introduction

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1.1 Organocatalysis

For many decades scientists have been stimulated by the exquisite manner and elegance in which Nature produces complex chiral molecules with impressive levels of selectivity and specificity. Endeavours by synthetic chemists have elegantly demonstrated the performance, selectivity and tuneability of bio- and transition metal-based catalysts to mediate a wide range of complex and enantioselective transformations. Only in recent decades has the use of small organic molecule catalysts (organocatalysts) emerged alongside the use of enzymes and metal-based complexes at the forefront of asymmetric catalysis. Despite sporadic reports of organocatalysed processes that date from the early 20th century, it was not until the late 1990s that organocatalysis was conceptualised and acknowledged as a general field with enormous potential, with the result being a rapid evolution in the reported application of organocatalysts in >100 discrete reaction types.[1] The remarkable recent growth observed in this area builds upon the exploratory findings of Bredig,[2] Pracejus,[3] Wynberg,[4] Hajos[5] and Wiechert,[6] Inoue,[7] Juliá and Colonna,[8] who all documented the use of cinchona alkaloid or amino acid derivatives as organic catalysts. However, the highly specific nature of these reactions, combined with poor mechanistic understanding, contributed to a slow realisation of the potential of organocatalysis as an approach to synthesis. These initial articles also did not emphasise the potential benefits of using organic molecules in catalysis, or the general concepts that underpin these reaction processes.

At the core of the modern interest in organocatalysis are the inherent advantages it presents to that of alternative enantioselective catalytic processes. Practically, most organocatalysts are insensitive to oxygen and moisture thus eliminating the need for strict experimental techniques, reagents, anhydrous solvents and equipment. From an economic standpoint, many organocatalysts are easy and cheap to prepare in large quantities, with most derived from chiral pool reagents and other single-enantiomer compounds available from Nature. Not only may this present lower process expenses for industrial projects but also lower costs for academic researchers entering the area of asymmetric catalysis. They can be used in a wide range of reaction processes for the preparation of diverse enantiomerically pure compounds of enormous complexity. Paramount to the development and widespread utilisation of catalysis in the modern day is the safety and environmental impact of these processes. One potential beneficial feature of small organic catalysts is their generally low/non-toxic effects with typically low levels of environmental damage.

To establish organocatalysis as a general catalytic concept it is necessary to determine and identify the key reactivity modes available. Improved understanding of these reactivity

modes allows us to apply organocatalysis to a wide range of examples in a systematic manner with predictable origins of selectivity. Commonly, the most powerful methodologies for enantioselective organocatalysis can be placed under the categories of Brønsted acid, Brønsted base, Lewis acid and Lewis base catalysis.

1.1.1 Brønsted Acid Catalysis

The role of a Brønsted acid catalyst is based on similar fundamentals to that of a Lewis acid catalysis whereby C=X bonds (where X is O, NR, CR_2) can be activated through non-covalent interactions with the reaction catalyst thus lowering the LUMO energy and increasing the electrophilicity of the substrate.[9] A proton is therefore considered the smallest and simplest Lewis acid, with the ability to activate the substrate in two ways (Figure 1). The first approach, referred to as general/neutral Brønsted acid catalysis, utilises a hydrogen bonding (H-bonding) interaction between the chiral catalyst (H-bond donor) and the substrate (H-bond acceptor) promoting selectivity during a nucleophilic attack on the substrate. The second approach, referred to as specific/stronger Brønsted acid catalysis, exploits the relative acidities of the chiral catalyst (Brønsted acid) and the substrate (Brønsted base) resulting in the formation of a tight ion pair that can impart enantioselectivity when attacked by a nucleophile. Typically, this second class of reaction is most effective at pH near or below the pK_{aH} of the substrate. In both these strategies it is believed that nucleophilic attack on the Brønsted acid activated species is the turnover-limiting step in the mechanistic cycle.

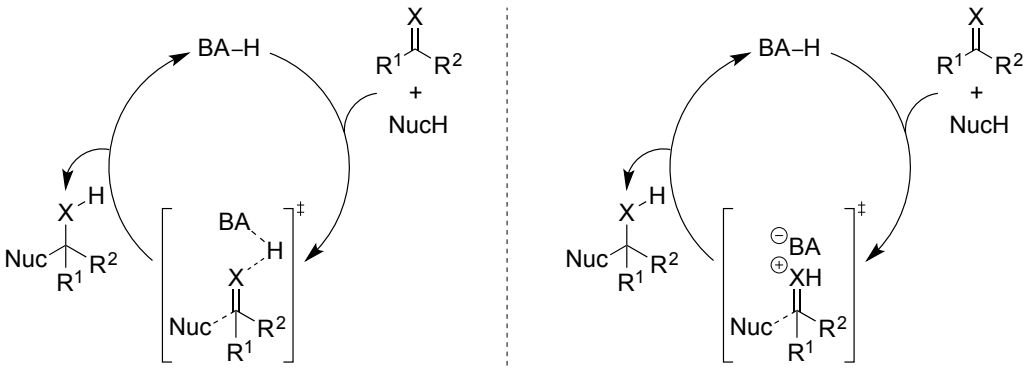
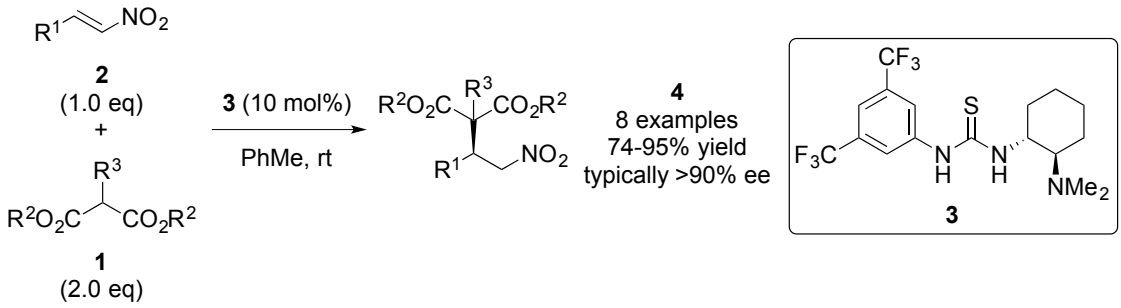


Figure 1 - General concepts for Brønsted acid catalysis.

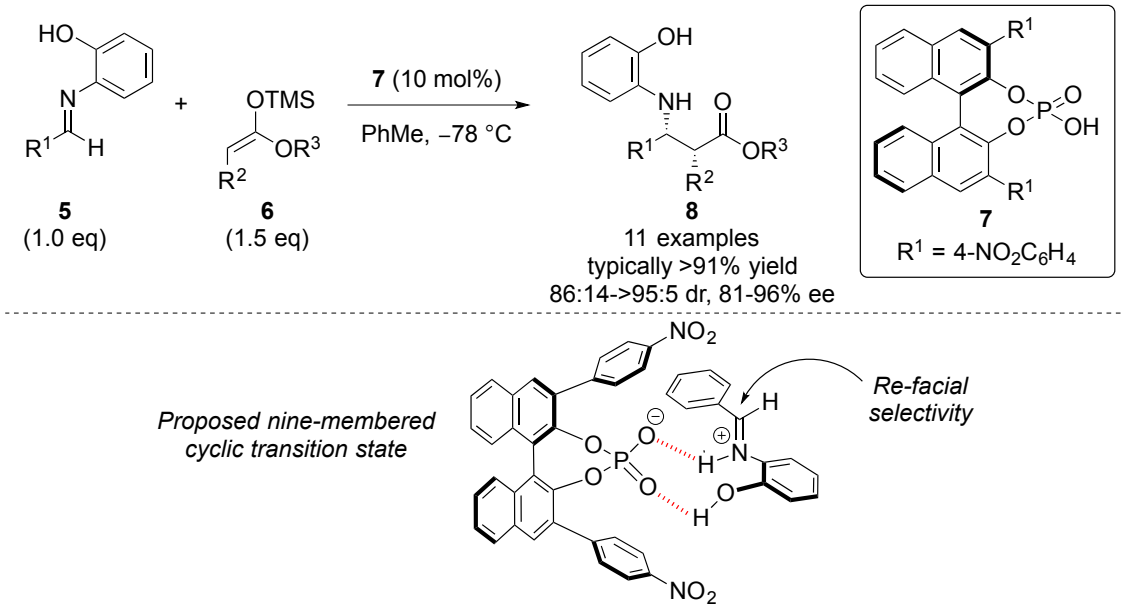
The research group of Takemoto has made a significant contribution to this area through the application of urea and thiourea-based H-bonding catalysts. One such prominent example is the enantioselective Michael addition of malonates **1** into nitroolefins **2** catalysed by thiourea **3** (10 mol%) (Scheme 1). The Michael adduct products **4** are provided in excellent yield (74-95%) and typically excellent enantioselectivity (>90% ee) for a range of aryl and alkyl substituted substrates.[10]



Scheme 1 - Enantioselective H-bonding catalysed Michael addition into nitroolefins.

The application of much stronger Brønsted acid catalysts that can protonate the substrate and form a close ion pair has attracted significant interest from the research community. The seminal work by Akiyama[11] and Terada[12] launched the development of a new class of chiral phosphoric Brønsted acid catalyst based upon the core structure of (*R*)-BINOL. These phosphoric acid catalysts are ideally designed to remain conformationally rigid, maximizing the communication of stereoselectivity to the substrate. A tightly associated ion pair between catalyst and substrate results from the high Brønsted acidity[13] of the P(O)O−H, with the phosphoryl P=O also available as a Lewis basic point of binding.[14] Various derivatives have emerged containing different stereodirecting groups situated at the *ortho*-position of the binaphthyl backbone that allows fine-tuning of enantioselectivity.

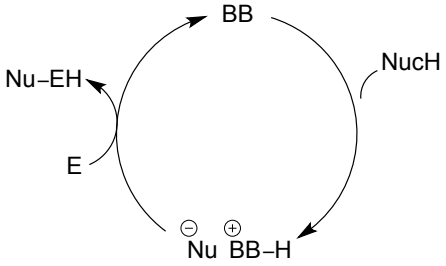
The founding work from Akiyama applies catalyst **7** (10 mol%) into the Mannich reaction between imines **5** and silyl enol ethers **6** to produce amino esters **8** with typically excellent levels of enantioselectivity (81-96% ee) (Scheme 2). The 2-phenol *N*-substituent on the imine is crucial for obtaining high enantioselectivity. Theoretical experiments have attributed the high enantioselectivity to the efficient association between the protonated imine and deprotonated catalyst **7** providing an ion-ion interaction, with a second favourable H-bonding interaction between phenol O−H and phosphoryl oxygen defining the *Re*-facial selectivity of the subsequent nucleophilic attack.



Scheme 2 - Phosphoric acid-catalysed enantioselective Mannich reaction.

1.1.2 Brønsted Base Catalysis

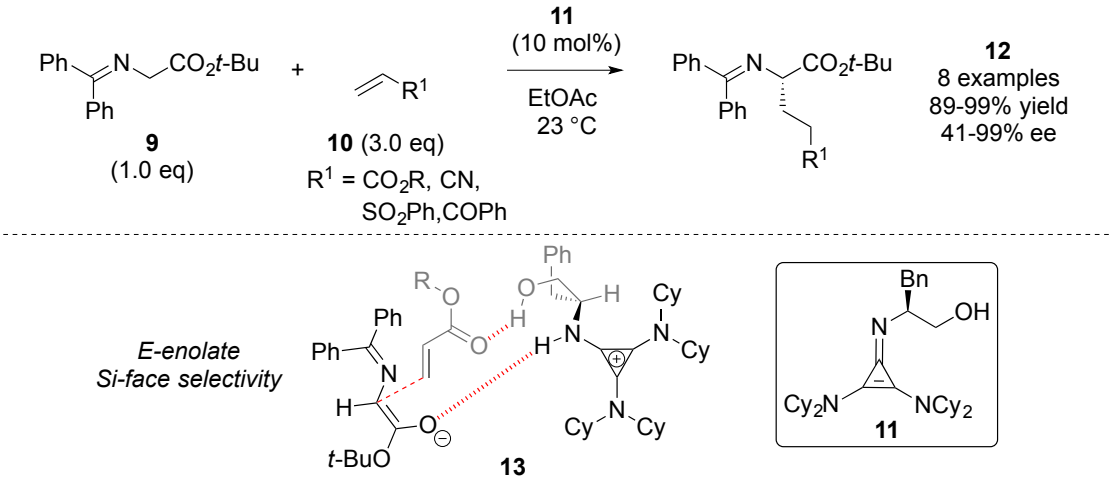
Deprotonation of a molecule by a Brønsted base constitutes a key step in many carbon−carbon and carbon−heteroatom forming reactions in organic synthesis. Classically, reactions instigated by a Brønsted base deprotonation of a substrate have been unselective. With the advent of asymmetric organocatalysis, a significant research direction has applied chiral Brønsted bases to mediate stereoselective transformations. The concept resides on the deprotonation of a pro-nucleophilic substrate (NuH) by a chiral Brønsted base catalyst (BB), generating a tight ion pair, which subsequently directs a bond-forming reaction in the presence of an electrophile (E) with induction of stereocontrol (Figure 2).[15] Catalyst design usually includes nitrogen-based functional groups with tertiary amines (most commonly cinchona alkaloids),[16] guanidines[17] and amidines[18] proving most abundant in research reports with properties of high basicity and moreover good accessibility from chiral pool reagents. In recent times, the preparation of bifunctional catalysts bearing both Brønsted base units (for nucleophile activation) and Brønsted acid units (for electrophile activation) has become widely researched.



Activation via deprotonation
Brønsted Base Catalysis

Figure 2 - General concepts of Brønsted base catalysis.

A transformation that has proven well suited for Brønsted base catalysis is the Michael addition of nucleophiles into α,β-unsaturated systems. A new and state-of-the-art method is the use of highly basic (pK_{BH+} = 26.9) cyclopropenimine compounds that present strong properties for application as Brønsted base catalysts. A modern example from Lambert uses cyclopropenimine catalyst **11** (10 mol%) to mediate the enantioselective Michael addition of glycine derived imines **9** into Michael acceptors **10** with high stereocontrol (89-99% ee) (Scheme 3).[19] Computational studies suggest the reaction to proceed *via* transition state **13**, with both the nucleophile and electrophile directed by the catalyst to dictate the excellent enantioselectivity of the reaction.[20]



Scheme 3 - Enantioselective Michael addition catalysed by cyclopreniminе catalyst 11.

1.1.3 Lewis Acid Catalysis

Activation of a substrate *via* metal-based Lewis acid catalysis is the foundation of many organic reactions. Through the maturity of organocatalysis, many of these functions have been revisited in recent times with the intention that organic Lewis acids can emulate the versatility and reactivity of their metal counterparts. Typically a chiral Lewis acid (LA) can activate a substrate (S) *via* the acceptance of a pair of electrons to form an associated adduct ($S^{+}{-}LA^{-}$) that can subsequently undergo a reaction and release the product (S−R) (Figure 3). To facilitate the need for a Lewis acid to have a vacant orbital to accept a lone pair of electrons, molecules such as ammonium, carbenium, silyl and phosphonium cations have attracted attention. Perhaps the most popular area to emerge within this area of Lewis acid organocatalysis is that of asymmetric phase transfer catalysis (PTC).[21]

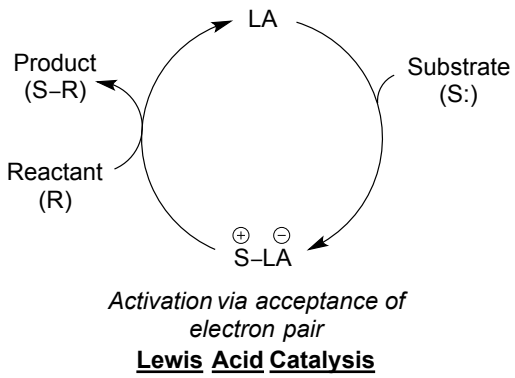
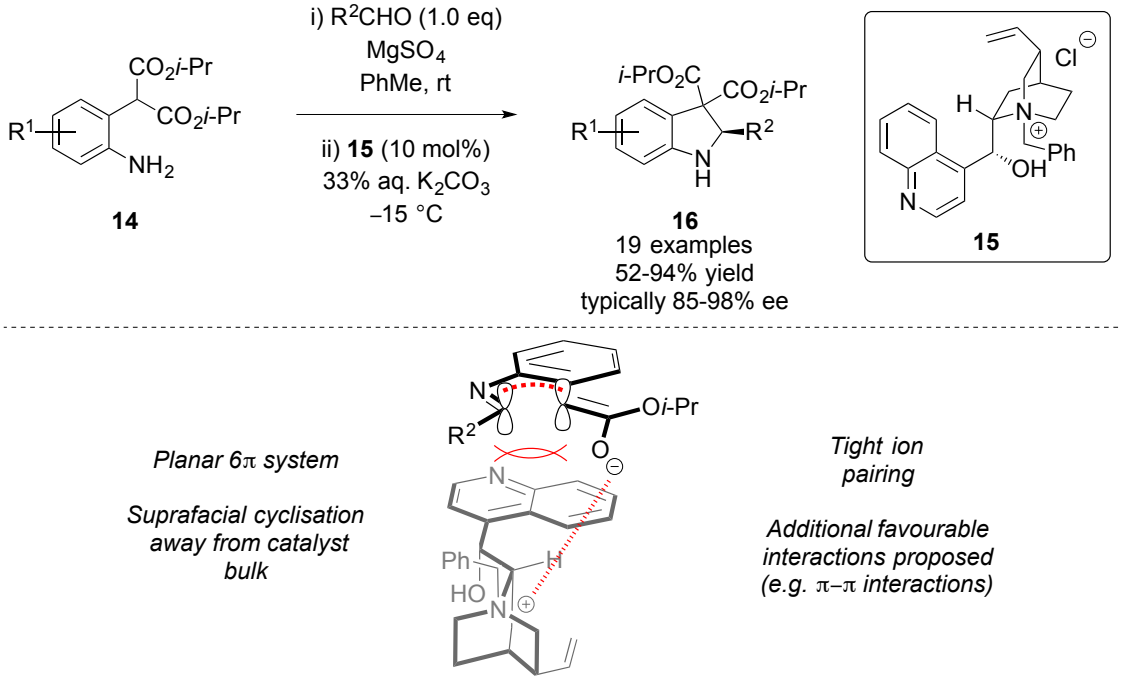


Figure 3 - General concepts of Lewis acid catalysis.

One PTC transformation studied recently by Smith and co-workers is enantioselective electrocyclisation.[22] Phase transfer catalyst **15** (10 mol%) can mediate the enantioselective 6π-electrocyclisation reaction of imines generated *in situ* from amines **14** and a range of aldehydes into indolines **16** with typically excellent stereoselectivity (85-98% ee). Stereochemical rationale has been assigned based on the tight ion pair model proposed by Corey and co-workers.[23] Inputting **14** into this model, it is proposed that the enolate oxygen forms a close association with ammonium catalyst **15** inducing a number of non-covalent interactions that dictate the torquoselectivity of the ring-closing step.



Scheme 4 - Enantioselective 6π-electrocyclisation reaction catalysed by 15 (one ester group removed for clarity).

1.1.4 Lewis Base Catalysis

Lewis base activation represents the largest area of organocatalysis and can be broadly defined as the ability of a Lewis base catalyst (LB) to activate a substrate (S) through the

donation of a lone pair of electrons (Figure 4).[24] Enhancement of a reaction occurs from the increased electron density present in the newly formed Lewis adduct ($LB^{+}-S^{-}$), how this electron density is distributed is determined by the constituent atoms and dictates the nucleophilic or electrophilic character of the reactive species when reacted with reactant (R) to form product (R−S). With a wide availability of chiral Lewis bases encompassing a number of complimentary reactivity modes, this field has progressed to the forefront of asymmetric catalysis.

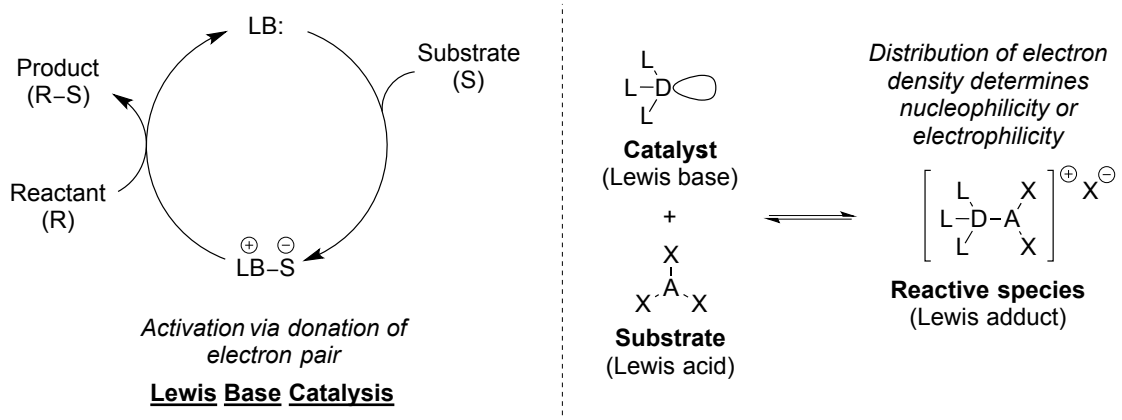


Figure 4 - General concepts of Lewis base catalysis.

Enamine Catalysis

Enamine catalysis consists of the condensation of a secondary amine catalyst with a carbonyl containing substrate, followed by deprotonation of the intermediate iminium cation to generate the key nucleophilic enamine species (Figure 5).[25] This newly formed enamine species has a raised highest occupied molecular orbital (HOMO) energy and therefore lower HOMO-LUMO energy gap compared to the starting ketone.

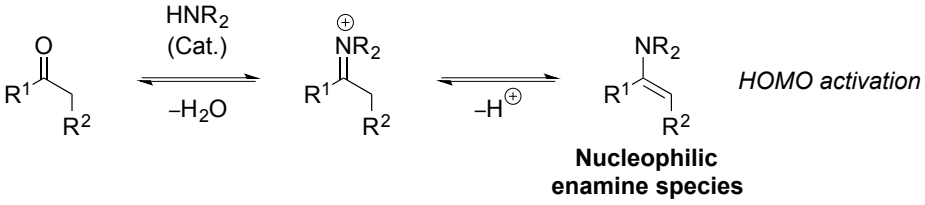
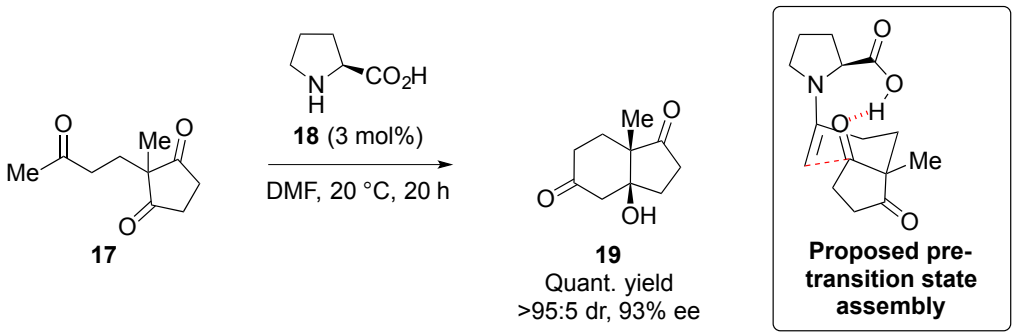


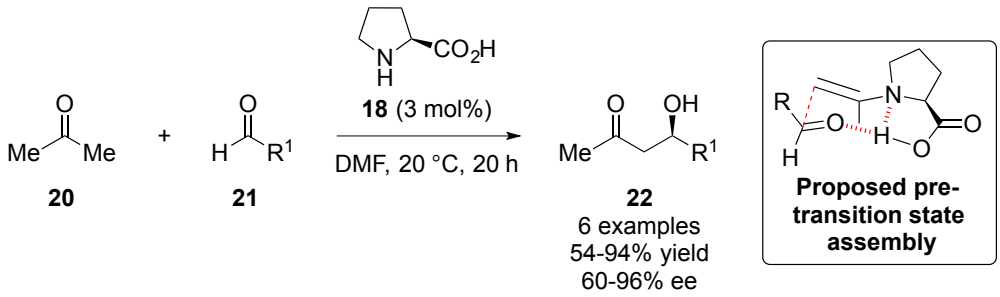
Figure 5 - Enamine formation by Lewis base catalyst.

Now realised as one of the first applications of asymmetric organocatalysis, the Hajos-Parrish-Eder-Sauer-Wiechert cyclisation reported in 1971 is one of the earliest examples of enamine catalysis (Scheme 5).[26] Enantioselective intramolecular aldol reaction of triketone **17** catalysed by (*S*)-proline **18** (3 mol%) gives bicyclic ketone **19** with excellent diastereo- and enantiocontrol (>95:5 dr and 93% ee). Following the generation of the enamine intermediate, it is proposed that the carboxylic acid substituent derived from (*S*)-proline **18** can H-bond with one of the ketone groups to define the selectivity of the cyclisation.



Scheme 5 - Hajos-Parrish-Eder-Sauer-Wiechert cyclisation

In 2000, List and co-workers revisited the use of the amino acid (*S*)-proline **18** in enamine catalysis with a piece of work that has since become celebrated as one of the founding examples of organocatalysis as a field in organic chemistry.[27] This work also displayed an enantioselective aldol reaction, but this time in a more challenging intermolecular system (Scheme 6). Applying acetone **20** as the enamine precursor with a range of aldehydes **21** catalysed by **18** (3 mol%) produces hydroxyl ketones **22** with typically moderate to excellent enantioselectivity (54-94% ee) and served as a solid proof of concept for the exploration of asymmetric enamine catalysis.



Scheme 6 - (*S*)-Proline-catalysed enantioselective aldol reaction.

Iminium Catalysis

Similarly to enamine catalysis, iminium catalysis involves the condensation of a secondary amine catalyst with a carbonyl containing substrate this time giving the electrophilic intermediate iminium cation (Figure 6). Here the key reactive species is LUMO activated, thus bringing the energy of the LUMO nearer to the HOMO of the nucleophile.[28]

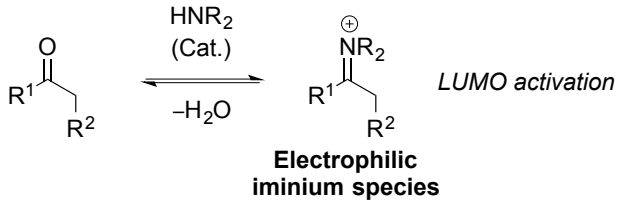
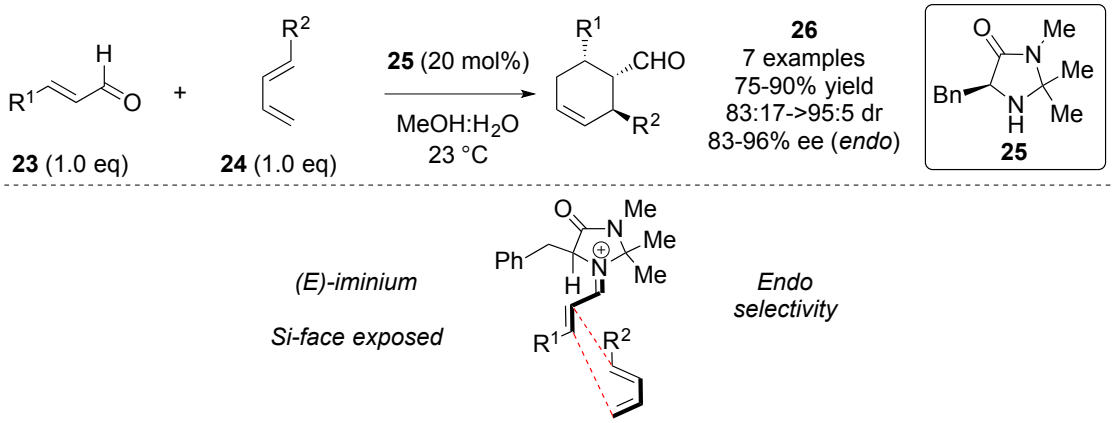


Figure 6 - Iminium formation by Lewis base catalyst.

In 2000, MacMillan and co-workers showed that the iminium intermediate generated from the condensation of imidazolidinone catalyst **25** (20 mol%) and enals **23** can be intercepted to give an enantioselective Diels-Alder reaction with dienes **24** (Scheme 7).[29] It's proposed that the geminal methyl groups on the catalyst favour the formation of an (*E*)-iminium ion, with the stereodirecting Bn substituent blocking the *Si*-face upon approach of the diene in an *endo* selective manner. Along with the prioneering enamine chemistry reported by List, this methodology was a founding example of the field of organocatalysis.



Scheme 7 - Iminium-catalysed Diels-Alder reaction.

SOMO Catalysis

Singularly occupied molecular orbital (SOMO) catalysis is one of the newest reactivity modes to enter the field of organocatalysis in recent years. The concept is based upon one electron oxidation of an electron-rich enamine, generated as described previously, to form a reactive radical cation with three π-electrons (Figure 7).[30] The electrophilicity of these SOMO intermediates allows them to react with a range of weak nucleophiles that are typically incompatible with other reactivity modes.

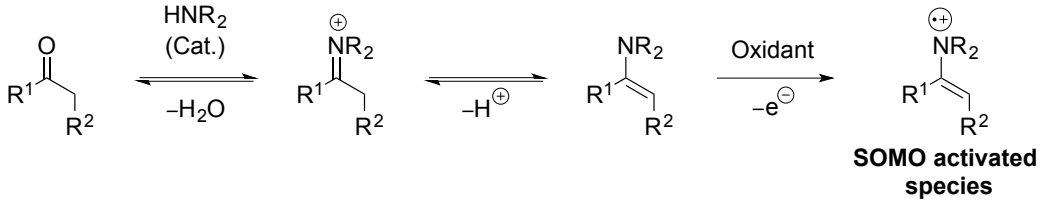
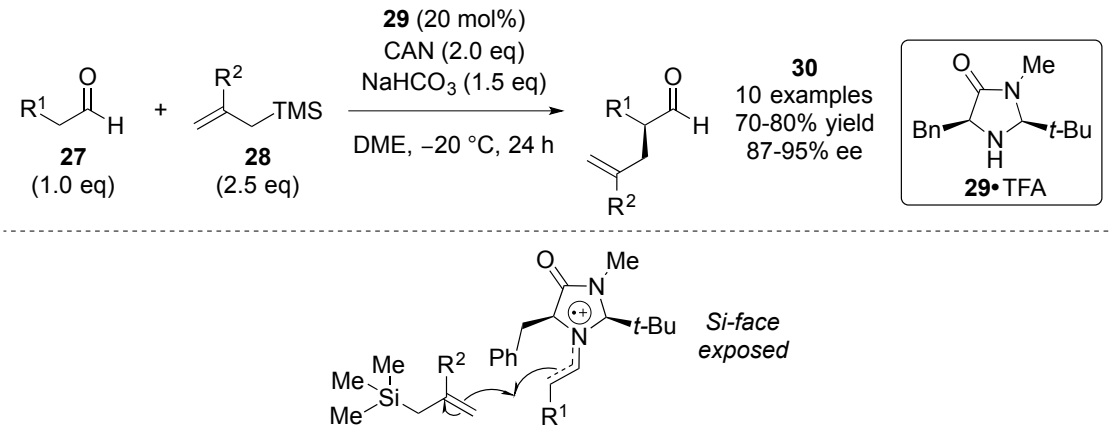


Figure 7 - Generation of SOMO activated intermediates.

The area of SOMO catalysis has been introduced and explored by the MacMillan group with their seminal work on the enantioselective α-alkylation of aldehydes (Scheme 8). Treatment of aldehydes **27** with imidazolidinone catalyst **29** (20 mol%) in the presence of allylsilanes **28** and ceric ammonium nitrate (CAN) as the oxidant gives products **30** in good yield (70-88%) and excellent enantioselectivity (87-95% ee). Computational studies suggest the (*E*)-configuration of the three π-system to minimise non-bonding interactions between the

catalyst *t*-Bu substituent and the substrate. Furthermore, enantiofacial discrimination arises from the blocking of the *Re* face by the benzyl group leaving the *Si*-face exposed for the reaction.



Scheme 8 - Enantioselective α-alkylation of aldehydes applying SOMO catalysis

1.1.5 Ammonium Enolate/Acyl Ammonium Catalysis

Nucleophilic tertiary amine catalysts have been classically used in a range of amidations, esterifications and acyl transfer reactions through their ability to effectively undergo *N*-acylation. In the last decade a number of research groups have elaborated on this function with the interception of a Lewis base generated *N*-acyl species with a selection of further transformations (Figure 8). Most commonly, the adopted focus is the complimentary methods of deprotonation of the *N*-acyl species to form a nucleophilic enolate equivalent or reaction of the *N*-acyl species as an *in situ* generated electrophile. Modern methods have utilised a number of chiral, non-racemic catalysts in these processes with the purpose of establishing enantioselective reactions.

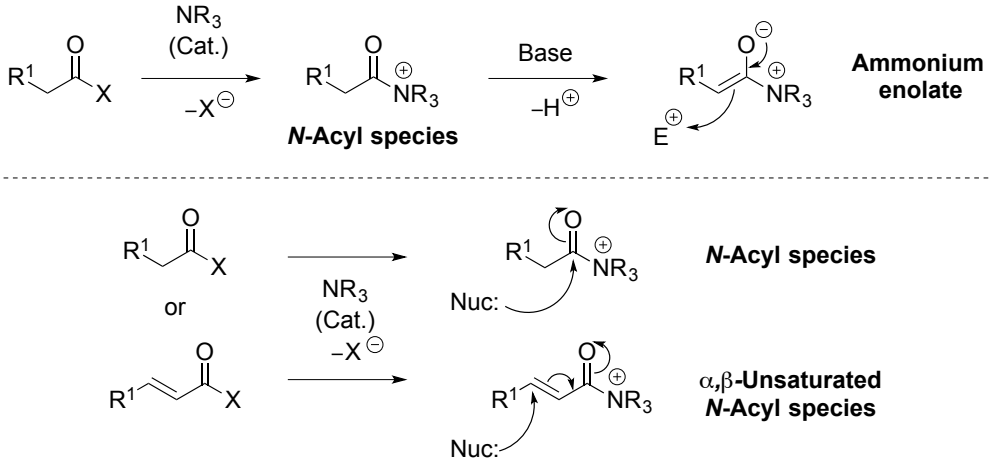


Figure 8 - Concepts of ammonium enolate and acyl ammonium catalysis.

Ammonium enolate catalysis

The generation of nucleophilic ammonium enolates can be considered closely related to that of Lewis base generated enamine species. However, many enamine catalysis methods are limited by the use of aldehydes and ketones as substrates with common functional groups such as esters, amides, carboxylic acids and nitriles proving incompatible in most cases. To expand the methodologies of organocatalytically generated enolate equivalents, a number of ammonium enolate strategies has been devised. As defined by Gaunt, there are three main branches of ammonium enolate catalysis dependent on the position at which the catalyst is covalently bonded to the substrate (Figure 9).[31]

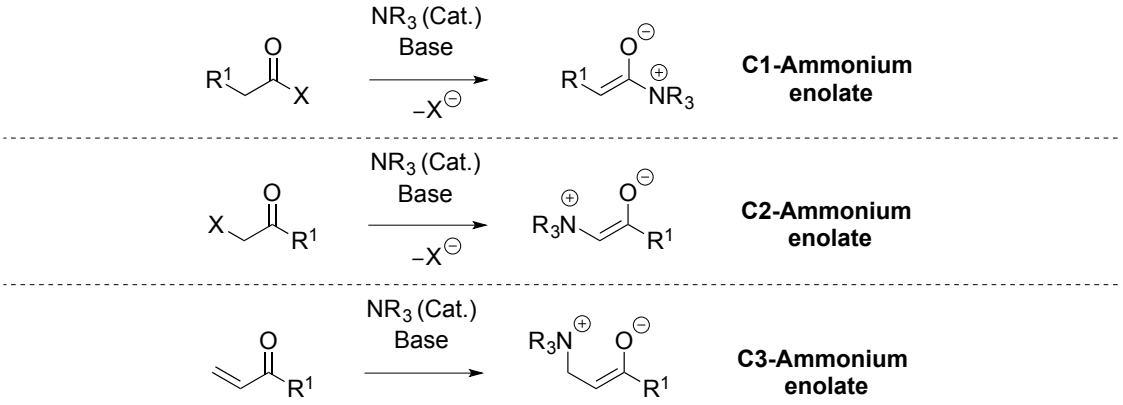
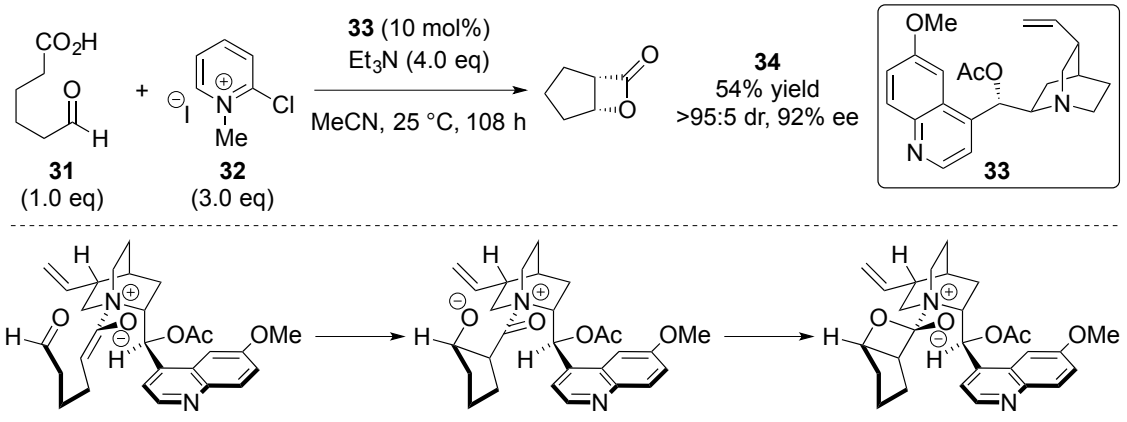


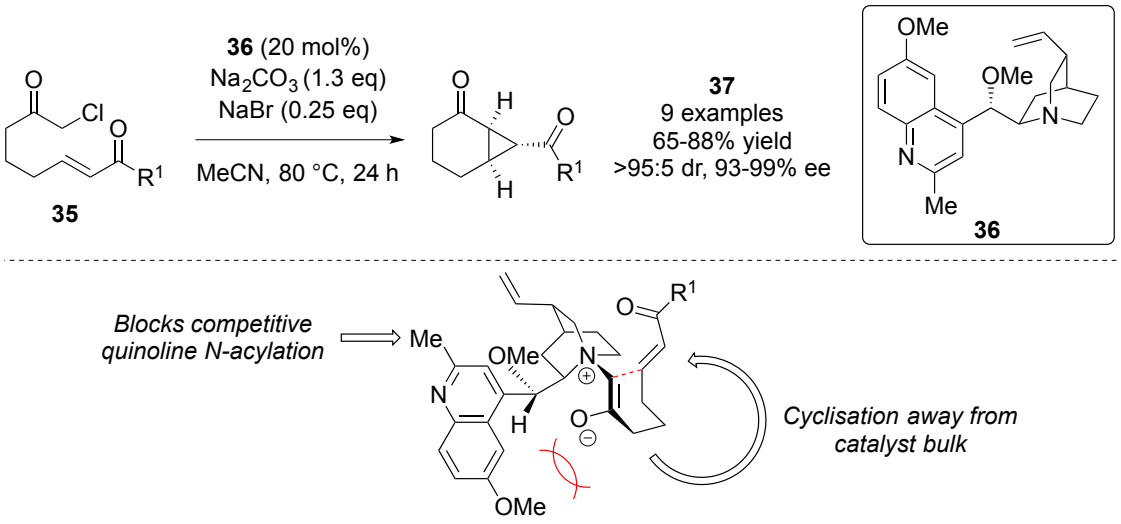
Figure 9 - Classification of ammonium enolates.

In 2001, Romo and co-workers showcased one of the first proof of principle reports that ammonium enolate catalysis could be used in asymmetric catalysis with high levels of enantiocontrol (Scheme 9).[32] Activation of carboxylic acid **31** with Mukaiyama's reagent **32** and treatment with *O*-acetyl quinidine catalyst **33** (10 mol%) and Et_3N promotes the intramolecular nucleophile-catalysed-aldol-lactonisation (NCAL) reaction to give bicyclic β-lactone **34** in excellent diastereo- and enantioselectivity (>95:5 dr and 92% ee). A proposed stereochemical model suggests the approach of the aldehyde onto the *Si*-face of the ammonium enolate leading to a *cis*-aldolate with ring closure of the oxetane.



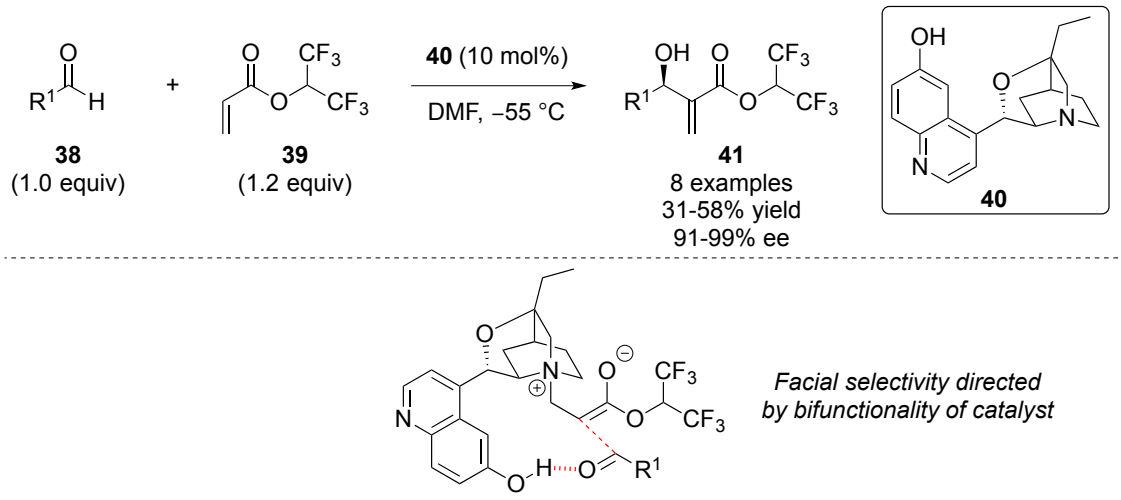
Scheme 9 - Nucleophile-catalysed-aldol-lactonisation reaction.

Enantioselective cyclopropanations *via* C2-ammonium enolate catalysis was reported by Gaunt and co-workers (Scheme 10). For example, the intramolecular cyclisation of diketones **35** catalysed by cinchona alkaloid **36** (20 mol%) gives bicyclic products **37** in typically good enantioselectivity (93-99% ee).[33] Following the isolation and X-ray crystal analysis of the intermediate *N*-acyl species, a proposed stereochemical rationale was shown with cyclisation occurring *via* a boat conformation onto the face opposite to the catalyst bulk. Further catalyst optimisation discovered that the inclusion of a methyl substituent at the 2-position of the quinolone heterocycle was necessary to deter any competitive quinoline *N*-acylation.



Scheme 10 - Cinchona alkaloid-catalysed intramolecular cyclopropanation.

C3-Ammonium enolate catalysis is slightly less explored than other organocatalytic reactivity modes, but a significant contribution has been made to the area of enantioselective Morita-Baylis-Hillman (MBH) reactions. Traditionally, MBH reactions with high enantioselectivity have proven difficult, however ammonium enolate routes have provided powerful advances in this area. An innovative example was reported by Hatakeyama and co-workers using β-isocupreidine **40** (10 mol%) as the catalyst, giving hydroxyl ester products **41** in excellent enantioselectivity and as one of the first examples of enantiomeric excesses >90% (Scheme 11).[34] Key for this reaction was the presence of the free hydroxyl group on the catalyst that can H-bond to the substrate, pre-organising the transition state toward the enantioselective reaction.



Scheme 11 - β-Isocupreidine 40-catalysed enantioselective Morita-Baylis-Hillman reaction.

1.2 Isothioureas as Lewis Base Organocatalysts

1.2.1 Development of Isothioureas as Organocatalysts

The use of the isothiourea motif in asymmetric synthesis draws its origins from the seminal work by Birman and co-workers on the kinetic resolution of secondary alcohols.[35] The work initially investigated the use of amidines as acyl transfer catalysts in the kinetic resolution of alcohol **42** using propionic anhydride (Figure 10). Good selectivity factors (*S*) were observed (*S* =28, *c* = 47%) with catalyst **45** and it was proposed that the pyridinium ring could offer a favourable π-stacking interaction within the transition state and hence explain the high enantioselectivity. Based on this proposal, annulated amidine **46** was trialled and gave slightly higher selectivity (*S* = 33, *c* = 51%). This study was extended to look at catalysts with the structurally related isothiourea scaffold. (−)-Tetramisole•HCl **47** is a commercial drug used to treat parasitic worm infections in animals and presents a cheap, readily available catalyst for asymmetric catalysis. Interestingly, the application of **47** provided comparable results with the amidines (*S* = 27, *c* = 45%), implying that the pyridinium ring in the amidine catalysts is not essential to obtain high selectivity factors. However, based on the previous proposal that π-stacking is an important feature in the selectivity of this reaction, (+)-benzotetramisole (BTM) was explored. The use of this benzannulated catalyst proved even more superior with improved enantiodiscrimination (*S* = 57, *c* = 49%).

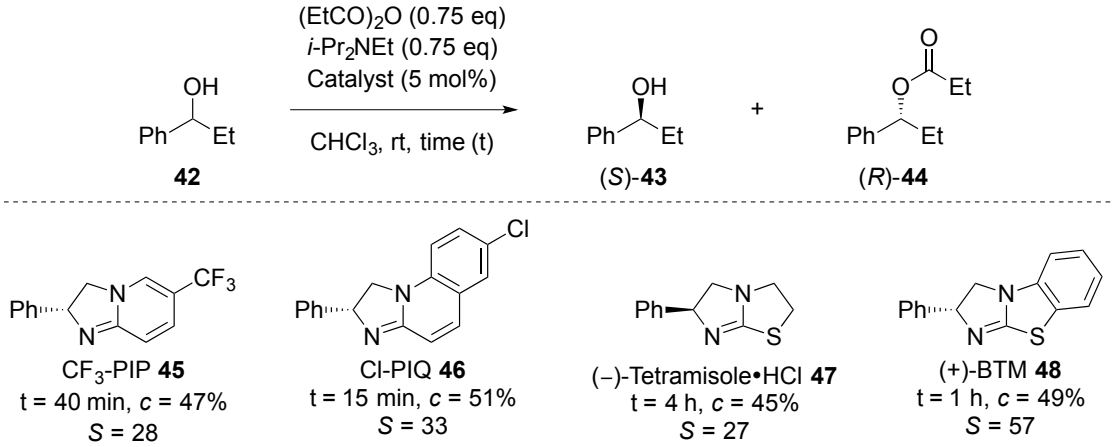


Figure 10 - Investigation into amidine and isothiourea-based catalysts in the kinetic resolution of 42.

From these initial studies it was clear that there exists a difference in reactivity and selectivity between amidine and isothiourea catalysts. It was proposed that the high selectivity from isothioureas originates from a stabilising interaction between the lone pair of the acyl ammonium oxygen and the σ* orbital of the C−S bond (Figure 11). This favourable interaction is believed to stabilise the transition state, leading to a more rigid conformation and higher enantiodiscrimination.

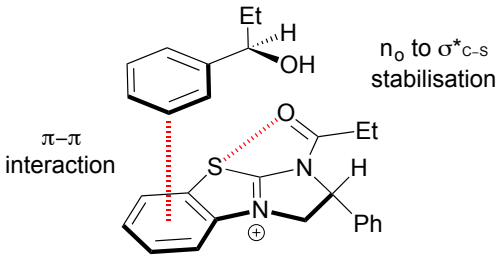


Figure 11 - Proposed transition state assembly for (+)-BTM catalysed kinetic resolution of 42.

This phenomenon has previously been reported in a number of systems where oxygen and sulfur are situated 1,5 to each other.[36] A notable example was the X-ray crystallographic results reported by Nagoa and co-workers with multiple (acylimino)thiadiazoline derivatives showing interatomic distances between oxygen and sulfur of 2.670 Å, which is smaller than the sum of their Van der Waals radii of 3.320 Å (Figure 12).[37] The resulting effect is a stabilising influence and a rigid *cis* conformation.

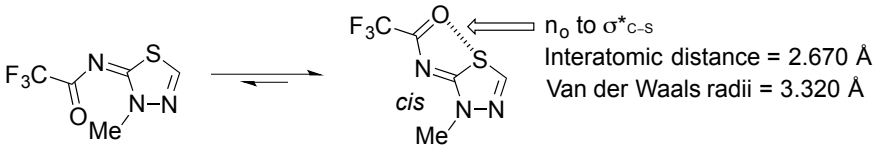


Figure 12 - Observed 1,5-S−O interaction in the X-ray analysis of (acylimino)thiadiazolines

Wu and Greer have conducted theoretical studies on this feature within the antitumor antibiotic, leinamycin (Figure 13). Density functional theory (DFT) calculations showed that the 1,5-S−O non-bonding interaction stabilises the conformation of the thiosulfinate ester heterocycle and leads to a lowering in energy of 6 kcalmol^{-1}.[38]

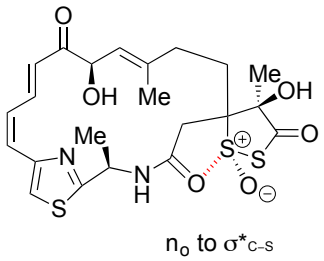
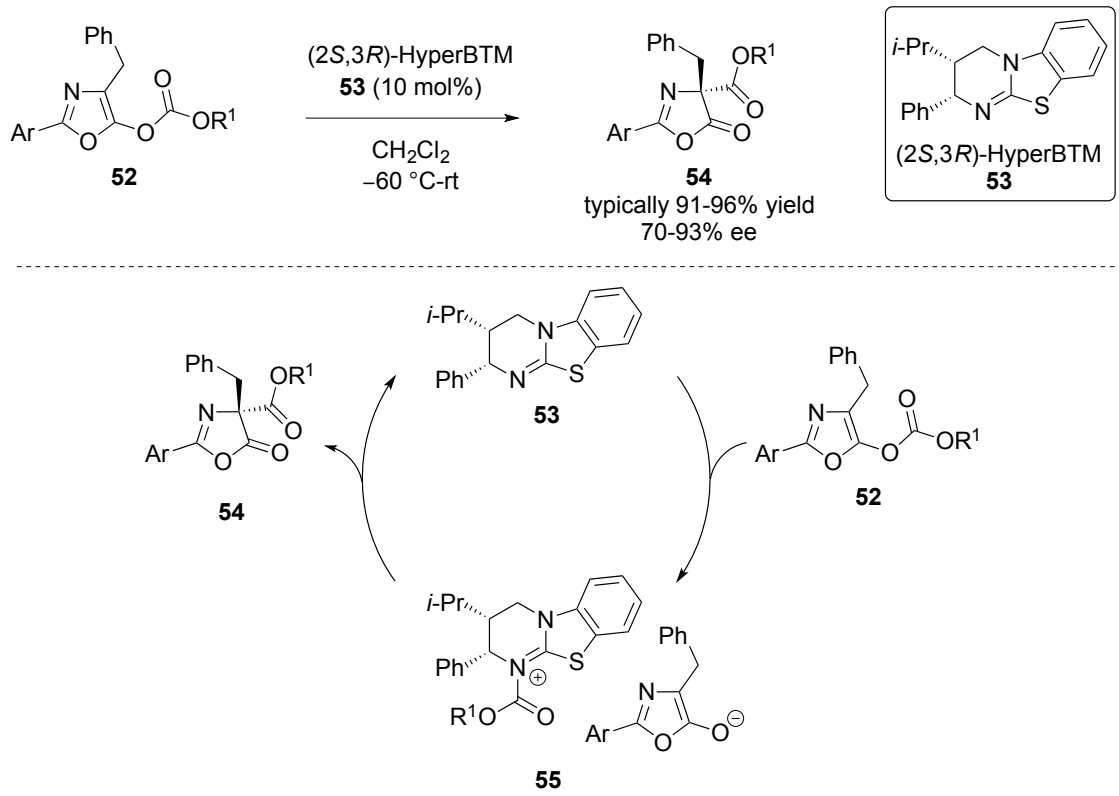


Figure 13 - Computational studies into the 1,5-S−O interactions in leinamycin.

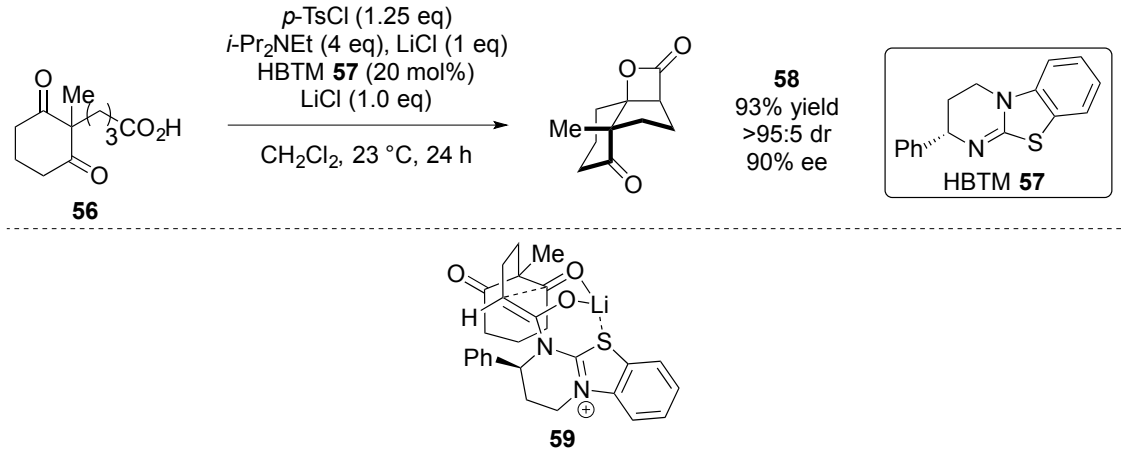
1.2.2 Application of Isothioureas within the Smith Group

Since the seminal work with isothioureas on the kinetic resolution of alcohols these powerful Lewis base catalysts have been applied to range of enantioselective processes, in particular by the Smith research group. An early transformation to be explored was the asymmetric Steglich rearrangement.[39] The isothiourea catalyst (2*S*,3*R*)-HyperBTM **53** (10 mol%) operates as an efficient carboxyl transfer agent in the rearrangement of oxazolyl carbonate **52** into *C*-carboxyazlactone **54** in good to excellent enantioselectivity (70-93% ee) and typically excellent yield (91-96%) (Scheme 12). The proposed mechanism starts with acylation of catalyst **53** *via* nucleophilic attack into the carbonate group of **52** to give ion-pairing **55**. Attack of the enolate through the C(4) position transfers the carboxyl group from the catalyst with enantiodiscrimination giving product **54**.



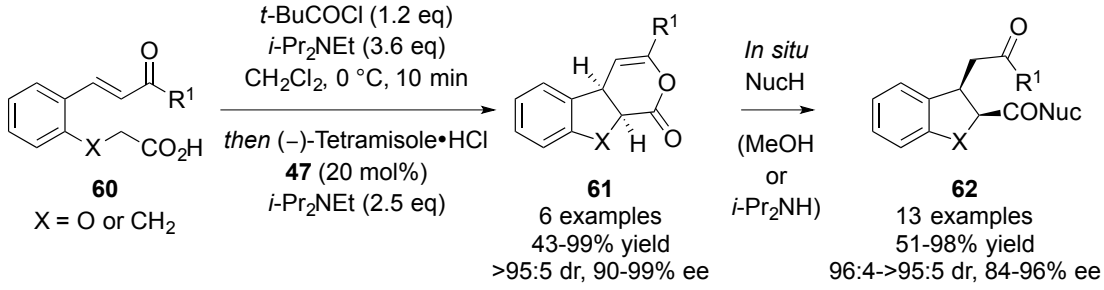
Scheme 12 - Isothiourea-catalysed Steglich rearrangement and proposed mechanism.

The Smith group has since expanded the use of isothiourea catalysts into the area of C1-ammonium enolate catalysis. The seminal work in this methodology arose in 2010 with the report from Romo and co-workers on the nucleophile-catalysed aldol lactonisation (NCAL) reaction of a range of cyclic tethered keto-acids (Scheme 13). One example involved the acid activation of **56** using *p*-tosylchloride and *i*-Pr_2NEt followed an aldol-lactonisation catalysed by the isothiourea homobenzotetramisole (HBTM) **57** (20 mol%) and using LiCl as an additive to give tricyclic lactone **58** in 93% yield, >95:5 dr and 90% ee.[40] It was proposed that in transition state **59**, the LiCl additive enforces the conformation *via* a Li−S chelation leading to higher enantioselectivity.



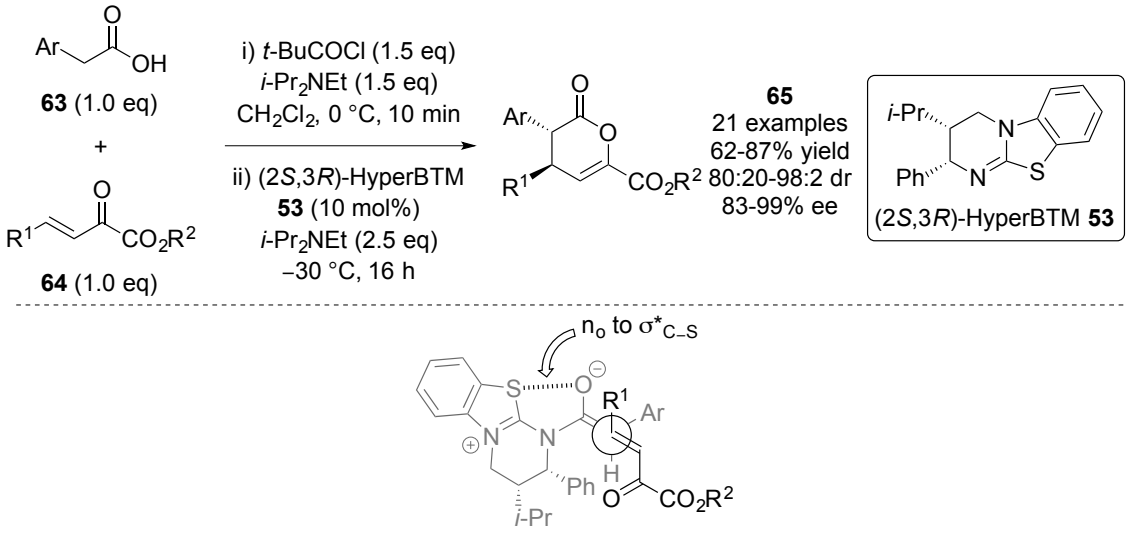
Scheme 13 - Isothiourea-catalysed enantioselective NCAL reaction.

At that time, the Smith group also published an isothiourea-catalysed intramolecular cascade with a Michael addition-lactonisation process (Scheme 14). Treatment of enone-acids **60** with *i*-Pr_2NEt, pivaloyl chloride and (−)-Tetramisole•HCl **47** (20 mol%) gives tricyclic dihydropyranones **61** in moderate to excellent yield (43-99%) and excellent stereoselectivity (>95:5 dr and 90-99% ee). A number of examples were subjected to an *in situ* ring opening with either MeOH or *i*-Pr_2NH to provide the corresponding dihydrobenzofurans and indanes **62** with maintenance of the high stereoselectivity.



Scheme 14 - Isothiourea-catalysed intramolecular Michael addition-lactonisation.

This work was also extended to a state-of-the-art application of C1-ammonium enolate catalysis with an intermolecular variant (Scheme 15).[41] Commercially available and bench stable aryl acetic acids **63** are used as enolate precursors through treatment with pivaloyl chloride, *i*-Pr_2NEt and isothiourea catalyst **53** (10 mol%). Addition of ketoester Michael acceptors facilitates a Michael addition-lactonisation cascade to afford *anti*-dihydropyranones **65** with excellent enantioselectivity. A key feature of isothiourea catalysts is the formation of a favourable oxygen to sulfur interaction (n_o to $\sigma^*_{C\text{-}S}$) that can stabilise and define the transition state assembly and account for the high stereocontrol.



Scheme 15 - Isothiourea-catalysed intermolecular Michael addition-lactonisation.

It's proposed that the mechanism begins with formation of mixed anhydride **66** from carboxylic acid **63**, *i*-Pr_2NEt and pivalolyl chloride (Figure 14). Interception of **66** with catalyst **53** gives acyl ammonium **67** that undergoes subsequent deprotonation to generate ammonium enolate **68**. In the presence of Michael acceptor **64**, this undergoes Michael addition to give **69** that cyclises to provide product **65** and regenerate the catalyst.

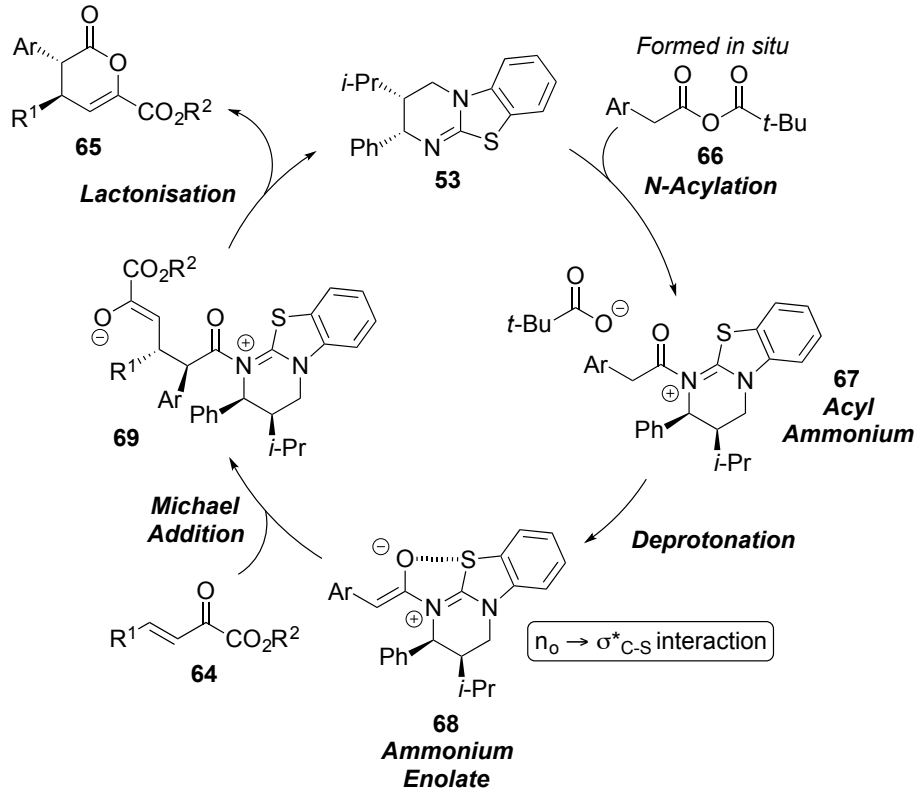


Figure 14 - Propsed mechanism for intermolecular isothiourea-catalysed Michael addition-lactonisation.

The methodology has proven broad in scope with a diverse range of carboxylic acids and electron-deficient Michael acceptors investigated giving a range of dihydropyranones,[42] dihydropyridinones[43],[44] and oxadiazinones,[45] all in excellent enantioselectivity (Figure 15).

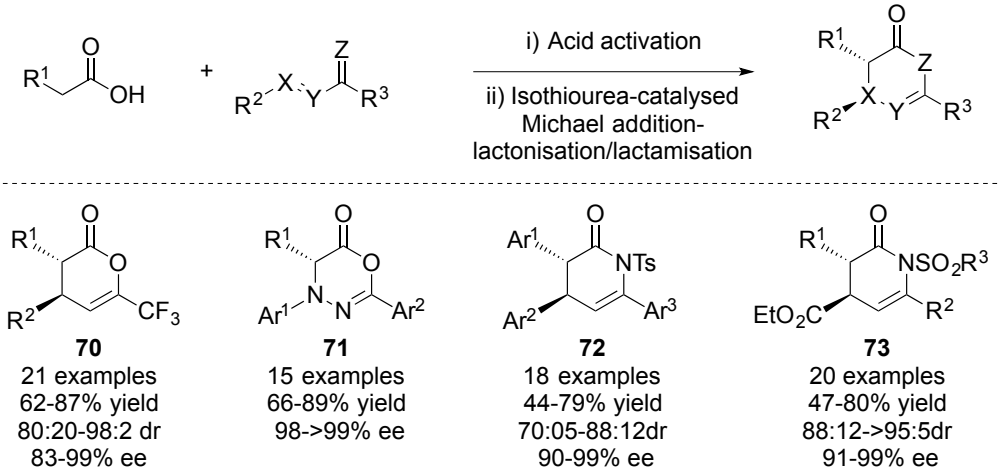
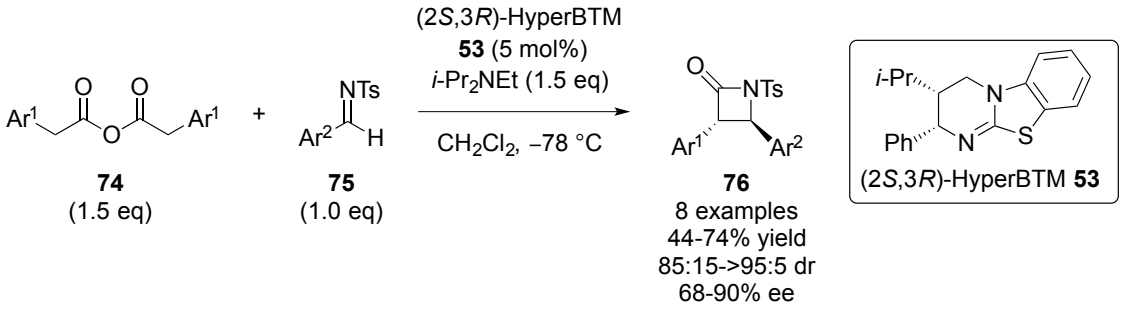


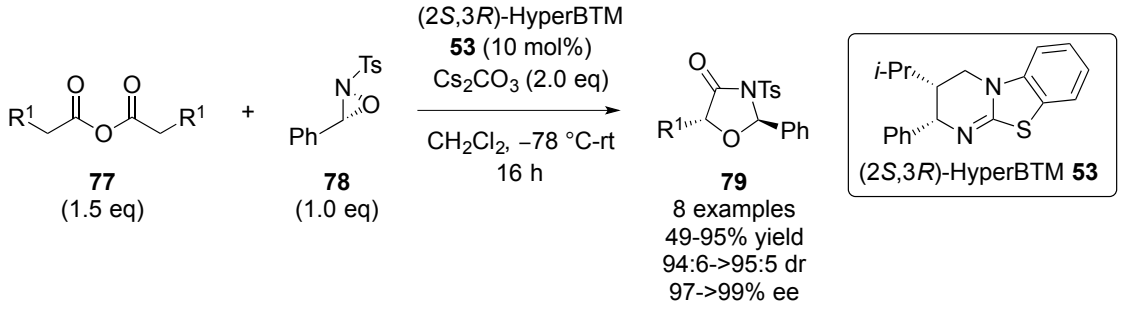
Figure 15 - Range of chiral heterocycles accessed using isothiourea-catalysed Michael addition-lactonisation/lactamisation protocol.

The process has also been expanded beyond that of formal [4+2] cycloaddition reactions to a formal [2+2] protocol (Scheme 16). In this system, the use of carboxylic acids as enolate precursors was problematic as purification of the desired products was difficult. Instead, homoanhydrides **74** were applied with (2*S*,3*R*)-HyperBTM **53** (5 mol%) and *i*-Pr_2NEt in the presence of aldimines **75** to give β-lactams **76** in moderate to good yield (44-74%), good to excellent diastereoselectivity (typically >95:5) and enantioselectivity (68-90% ee).



Scheme 16 - Enantioselective synthesis of β-lactams using isothiourea-catalysis.

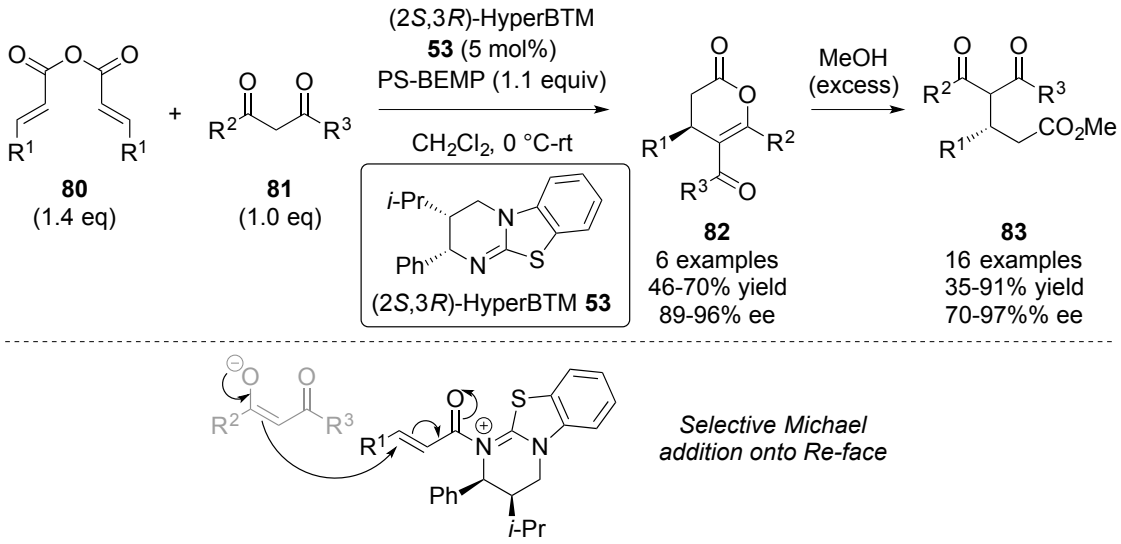
The use of isothiourea-generated enolates has also been applied to a formal [3+2] process with oxaziridine substrates (Scheme 17). Homoanhydrides were also tried in this system due to side-reactions occurring from a carboxylic acid and pivalolyl chloride activation method. Reaction of homoanhydrides **77** with (*R*,*R*)-oxaziridine **78**, Cs_2CO_3 and (2*S*,3*R*)-HyperBTM **53** (10 mol%) gave the corresponding products **79** in moderate to excellent yield (49-95%) and typically excellent diastereoselectivity (94:6->95:5 dr) and excellent enantioselectivity (97->99% ee).



Scheme 17 - Enantioselective isothiourea-catalysed synthesis of oxazolidin-4-ones.

In the context of asymmetric catalysis the use of acyl ammonium species is relatively new with much of the attention directed towards α,β-unsaturated acyl species that can undergo enantioselective Michael addition reactions. A primary methodology in this area was displayed by Smith and co-workers in 2014 (Scheme 18).[46] Reaction of isothiourea catalyst **53** (5 mol%) with homoanhydrides **80** gives an intermediate α,β-unsaturated acyl ammonium species that can be attacked by diketones **81** in an enantioselective Michael addition at the *Re*-face, with

subsequent proton transfer and lactonisation giving dihydropyranones **82** in excellent enantioselectivity (89-96% ee) with many examples being subject to an *in situ* ring opening to provide products **83** (where $R^2 = R^3$).



Scheme 18 - Application of isothiourea-generated α,β-unsaturated acyl ammonium intermediates.

1.3 Aims of the Project

Isothiourea-generated enolate equivalents can provide a powerful strategy for the construction of chiral heterocycles with high levels of stereocontrol. However, at the beginning of this PhD, there was no truly organocatalytic formal cycloaddition processes for the synthesis of functionalised heteroaromatics. Based on the absence of such methodologies, the initial aim of this work was to create efficient, organocatalytic protocols for the preparation of heteroaromatic products of biological relevance. It was proposed that C1-ammonium enolates derived from cheap, readily available carboxylic acid precursors would form appealing building blocks for this undertaking. Additionally, with the still ever growing need for stereodefined molecules and highly enantioselective catalytic processes to provide them, it was also intended to target further chiral heterocyclic products using isothiourea-catalysed Michael addition-cyclisation processes. Through variation in the substrates applied to this method, the scope, stereoselectivity and robustness of such systems can be assessed.

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Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 2: One-Pot Synthesis of 2,4-Substituted Pyridine 6-Sulfonates

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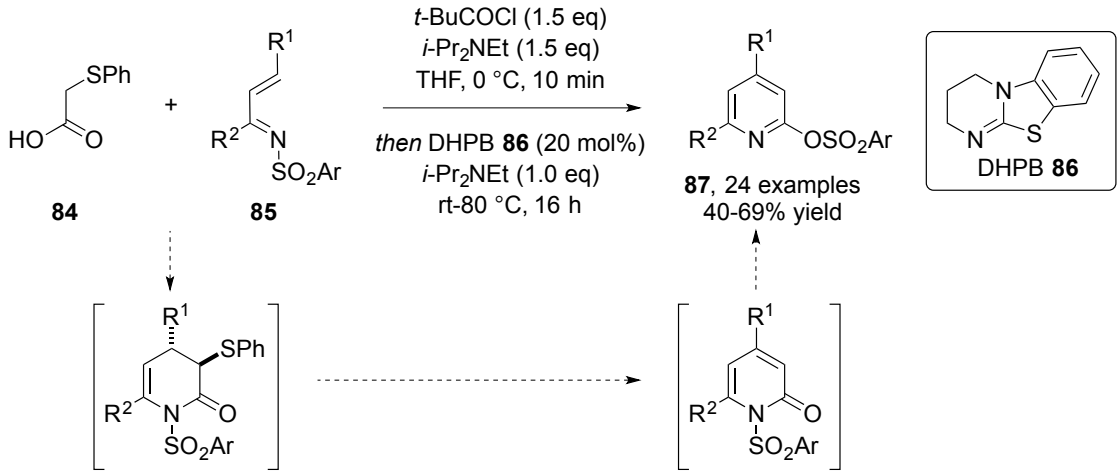
Chapter 2: One-Pot Synthesis of Functionalised Pyridines

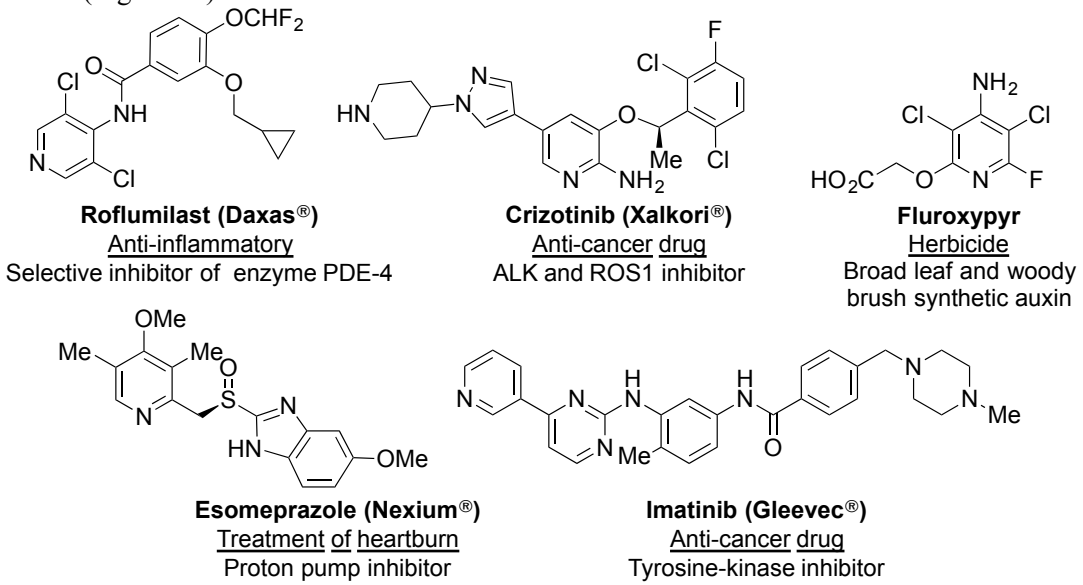
This chapter describes the discovery of a one-pot Lewis base-mediated procedure for the preparation of 2,4,6-substituted pyridines. This one-pot organocatalytic cascade is broad in scope and incorporates a synthetically valuable functional handle that can be easily derivatised. The cascade reaction is initiated with a DHPB **86** catalysed Michael addition-lactamisation between (phenylthio)acetic acid **84** and α,β-unsaturated ketimines **85** in the presence of pivaloyl chloride and *i*-Pr_2NEt, giving the corresponding dihydropyridinone, which readily undergoes elimination of PhSH and a thermal-assisted *N*- to *O*-sulfonyl transfer affording functionalised pyridine sulfonates **87** (Scheme 19).[47]



Scheme 19 - Isothiourea-catalysed one-pot synthesis of functionalised pyridines.

2.1 Introduction

The pyridine motif is a heterocyclic class present at the core of many biologically active molecules and has found widespread function within many agrochemical and pharmaceutical products (Figure 16).[48]



Roflumilast (Daxas®)
Anti-inflammatory
Selective inhibitor of enzyme PDE-4

Crizotinib (Xalkori®)
Anti-cancer drug
ALK and ROS1 inhibitor

Fluroxypyr
Herbicide
Broad leaf and woody brush synthetic auxin

Esomeprazole (Nexium®)
Treatment of heartburn
Proton pump inhibitor

Imatinib (Gleevec®)
Anti-cancer drug
Tyrosine-kinase inhibitor

Figure 16 - Biologically relevant pyridine molecules.

Specifically, the pyridine core has found a prevalent place within many of the top commercially approved pharmaceuticals. A recent study by Njardarson and co-workers explored the structural trends within a database of 1,086 U.S. FDA-approved drugs, and found that 59% of all small molecules contain a nitrogen heterocycle. Pyridine features in this list as the second most abundant heterocycle behind piperidine hence making it the most prevalent heteroaromatic motif (Figure 17).[48b]

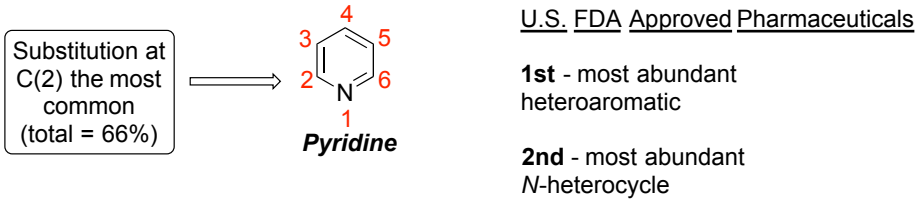


Figure 17 - Prevalence of pyridine within U.S. FDA-approved pharmaceuticals.

2.1.1 Classical Routes to Synthesise Functionalised Pyridines: Condensation Reactions

Due to the privileged status of these heterocycles there has been much attention directed towards new methodologies that can provide these molecules efficiently and in high yield.[49] Classical routes to construct pyridines focused on the condensation of carbonyl compounds with a nitrogen source. Historical examples include the [5+1] condensation,[50] Hantzsch ester pyridine synthesis,[51] and also the [3+2+1] condensation (Figure 18).[52]

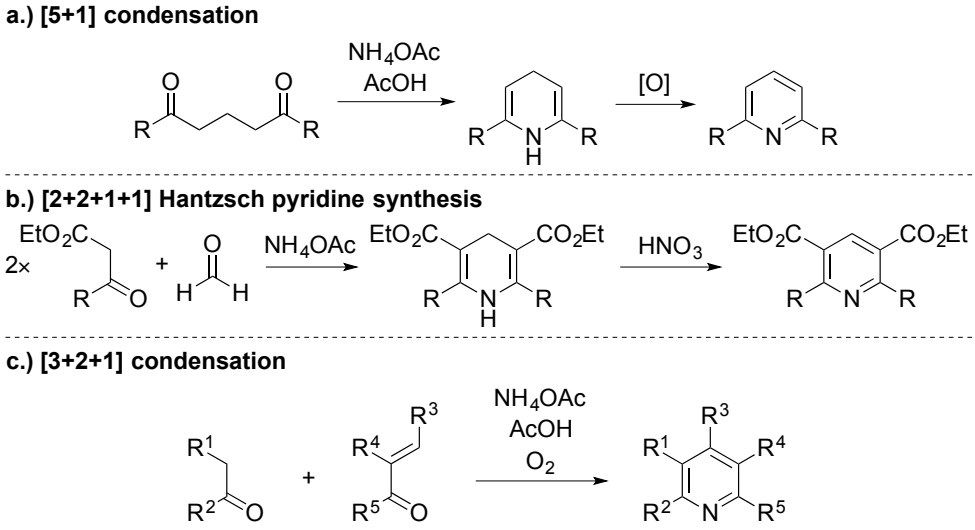
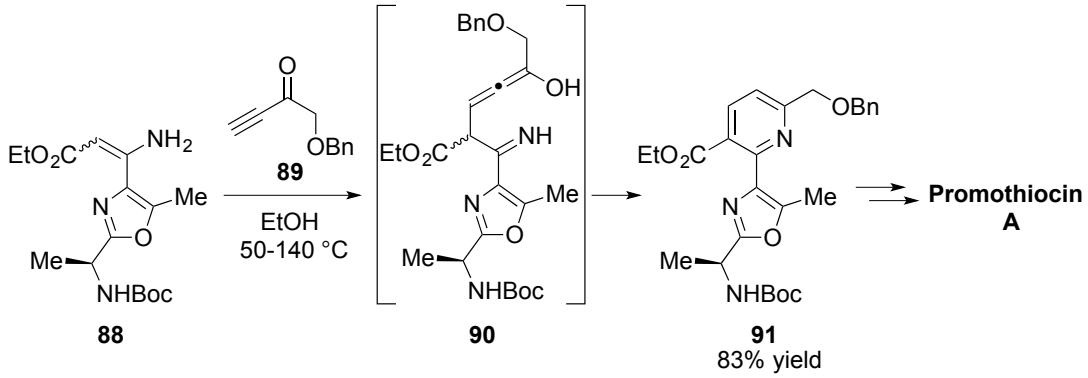


Figure 18 - Classical and early condensation routes towards the synthesis of pyridines.

Condensation approaches such as the Bohlmann-Rahtz synthesis have been used in recent times by Moody and co-workers in their successful synthesis of promothiocin A (Scheme 20).[53] After the preparation of the oxazole amino ester **88**, alkynone **89** was added in EtOH at

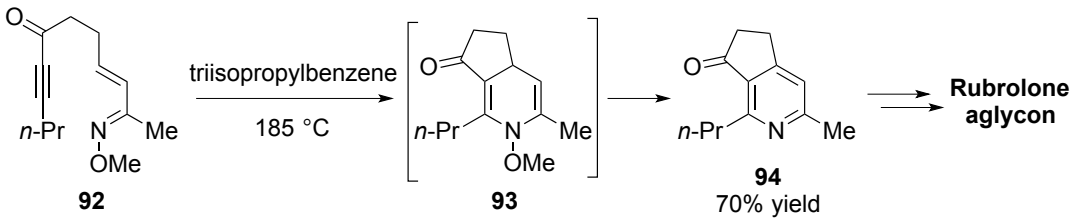
50 °C to give conjugate addition intermediate **90**. Increasing the temperature to 140 °C resulted in cyclisation to give pyridine **91** in 83% yield.



Scheme 20 - Bohlmann-Rahtz reaction used in the synthesis of promothiocin A.

2.1.2 Classical Routes to Synthesise Functionalised Pyridines: Cycloaddition Strategies

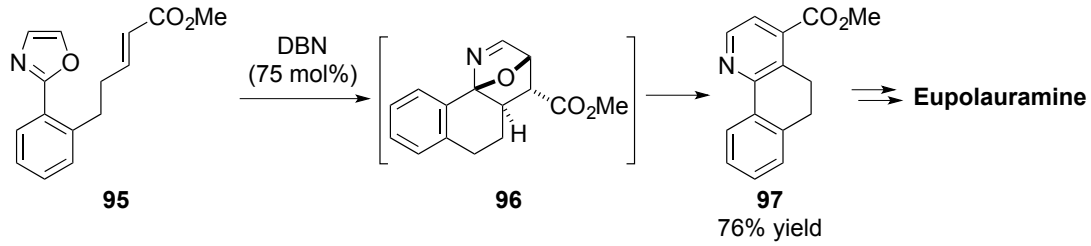
Cycloaddition chemistry is an effective tool for building cyclic structures, its use as a strategy to produce pyridines should therefore be considered. For example, Diels-Alder reaction between an alkene (or alkyne) and an azadiene, followed by oxidation into the desired pyridine is conceivable but examples are rare. This strategy commonly encounters a number of difficulties originating from various disfavoured electronic, conformational and thermodynamic issues found with the pericyclic reaction. As a result, modifications have been developed that incorporate electron-donating substituents onto the nitrogen of the azadiene. This gives a more electron-rich azadiene, which is preferable for a conventional Diels-Alder reaction and additionally allows elimination of this group to facilitate the final formal oxidation into the pyridine. As a representative example of this strategy, Boger and co-workers applied this methodology to the synthesis of Rubrolone aglycon (Scheme 21).[54] Exposure of azadiene **92**, bearing the N-OMe functionality, to high temperatures (185 °C) gave pyridine **94** in 70% yield *via* intermediate **93**, followed by elimination of MeOH.



Scheme 21 - Cycloaddition-elimination strategy applied by Boger and co-workers.

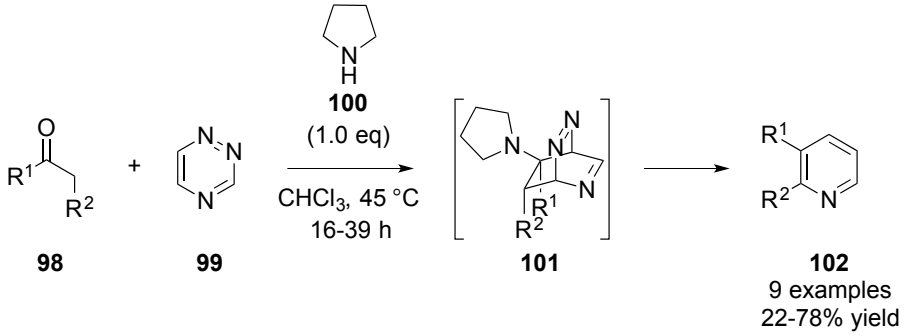
The most commonly-applied strategy involves an inverse electron demand Diels-Alder reaction followed by extrusion.[55] One notable example arose from Weinreb and co-workers in their synthesis of eupolauramine in 1984 (Scheme 22).[56] Oxazole **95** underwent an intramolecular hetero Diels-Alder reaction to give intermediate adduct **96**. This species was then dehydrated to provide pyridine **97** in 76% yield. Applying oxazoles in this approach is

commonly referred to as the Kondrat'eva reaction.[57],[58] The use of oxazoles in this manor can, however, lead to complex product distributions occurring from multiple possible fragmentations of the oxo-bridged intermediate or other potential side-reactions.



Scheme 22 - Kondrat'eva reaction used in the synthesis of eupolauramine.

More common is the use of heterocycles assigned to the 6-membered nitrogen containing structural family. Pyrimidines, for example, are capable of undergoing Diels-Alder/retro-Diels-Alder sequences with regioselectivity dependent on the substituents present.[59] Related attempts using pyridazine are known, although not as prevalent. Perhaps the most useful protocol in this area is to apply 1,2,4-triazines, as these readily undergo inverse electron demand Diels-Alder reactions with a wide range of electron-rich dienes. Boger and co-workers have made a prominent contribution to this approach (Scheme 23).[60] Treatment of ketone **98** with pyrrolidine **100** generates an enamine *in situ* that subsequently reacts in an inverse electron demand hetero Diels-Alder reaction with triazine **99** to give adduct **101**. This intermediate then collapses with extrusion of N_2 and elimination of pyrrolidine **100** to provide pyridine **102** in typically moderate to good yields.

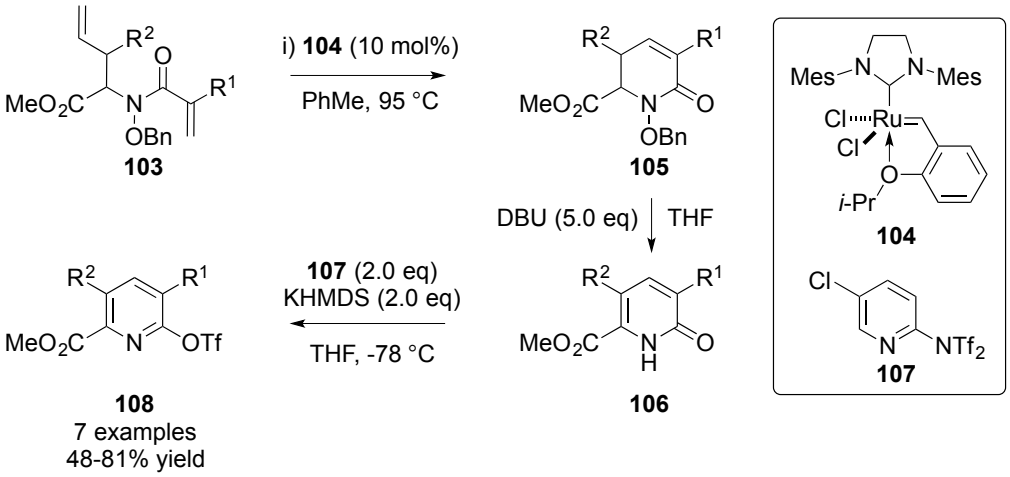


Scheme 23 - Boger pyridine synthesis.

2.1.3 Modern State-of-the-Art Strategies for the Synthesis of Functionalised Pyridines

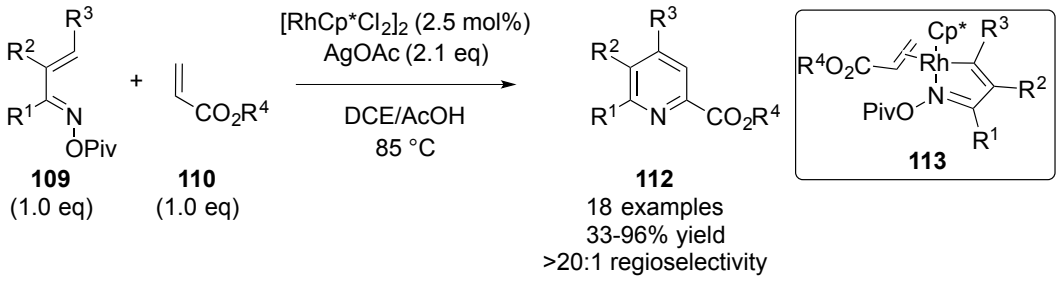
With many stoichiometric methods established, the largest drive in this area has been towards the development of efficient catalytic methodologies. Predominantly, many transition metal-catalysed processes have dominated the area of pyridine synthesis over the last decade. Notably, the emergence of ring-closing metathesis (RCM) has allowed further routes to construct the cyclic pyridine framework. Donohoe and co-workers reported an example where an RCM approach was used to access dihydropyridones, which can subsequently be

transformed into 2,6-substituted pyridines **108** (Scheme 24). RCM of oxime ester **103** with Hoveyda-Grubbs second generation catalyst **104** gives dihydropyridone **105**.[61] Treatment of **105** with DBU promotes elimination to give pyridone **106** that, following triflation with Comin's reagent **107**, yields pyridine **108** in excellent yield.



Scheme 24 - Pyridine formation *via* RCM step-wise protocol.

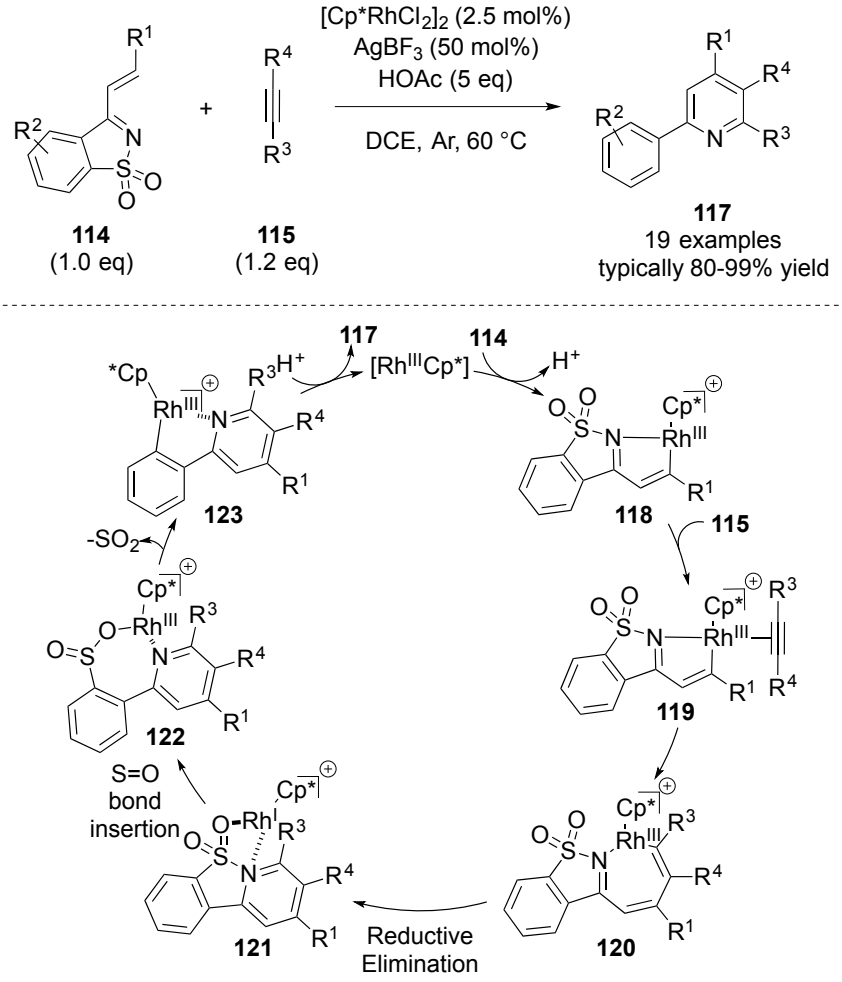
In 2013 Rovis and co-workers described a Rh(III)-catalysed [4+2] cycloaddition protocol for the synthesis of 2,3,4,6-substituted pyridines (Scheme 25).[62] Reaction of pivaloyl ketoxime **109** and olefin **110** with catalyst $[RhCp^*Cl_2]_2$ **111** and AgOAc proceeds, *via* rhodacycle **113**, to give substituted pyridine **112** in typically high yield. This work provides an excellent method for the rapid construction of pyridines with excellent regioselectivity (>20:1 for all examples).



Scheme 25 - Rh(III)-catalysed pyridine construction.

More recently Dong and co-workers have reported a further Rh-catalysed pyridine synthesis.[63] C−H activation of sulfonyl ketimine **114** with Rh-catalyst **116** and subsequent formal cycloaddition with alkyne **115** produces pyridine **117** in excellent 80-99% yields (Scheme 26). Coordination of the Rh catalyst to the imine nitrogen of **114** allows for C−H activation at the β-position giving rhodacycle **118**. Subsequent coordination of **115** to the Rh species promotes an alkyne insertion into the C−Rh bond of **119** to generate intermediate **120**. Following reductive elimination, the catalytic process is proposed to proceed *via* chelation of the sulfonyl group to the Rh(I) centered species **121** with subsequent S=O insertion to **122** and

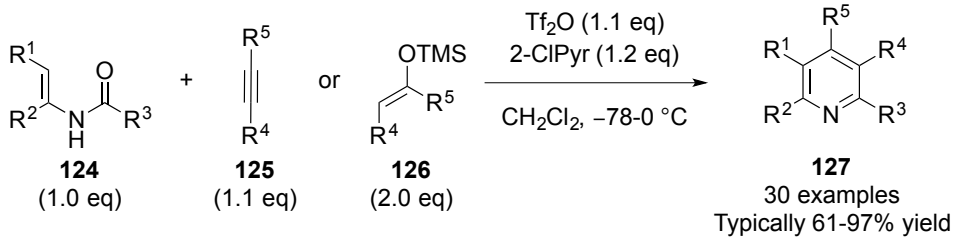
cleavage of the N−S bond to give **123**. During this step, the Rh(I) species **121** may be oxidized to give Rh(III) **122** with sulfur reduced from oxidation state (VI) to (IV). This suggests the N−S bond is acting as an internal oxidant. Finally, the Rh species can dissociate by protonolysis to give pyridine **117**.



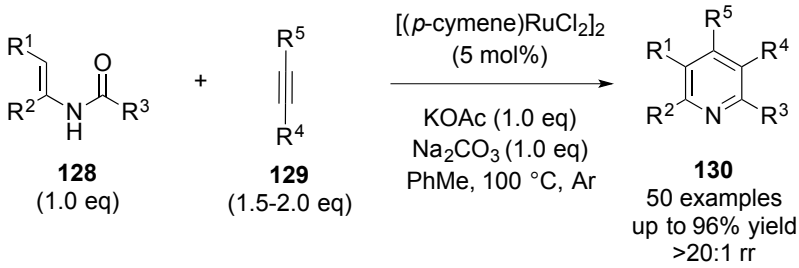
Scheme 26 - Synthesis of pyridines using Rh-catalysis and *N*-sulfonyl ketimines and proposed mechanism.

Following the report from Movassaghi and co-workers[64] in 2007 on the application of enamides towards the synthesis of polysubstituted pyridines (Scheme 27a), the group of Wang[65] successfully developed a catalytic protocol, also from enamides (Scheme 27b). The procedure applies a formal dehydrative [4+2] cycloaddition using enamides **128** and alkynes **129**, catalysed by $[(p\text{-cymene})RuCl_2]_2$, giving pentasubstituted pyridines **130** in typically excellent yield. The scope of this reaction is broad and includes many highly functionalised pyridines and a number of polycyclic or annulated examples.

a.) Movassaghi and co-workers - 2007.

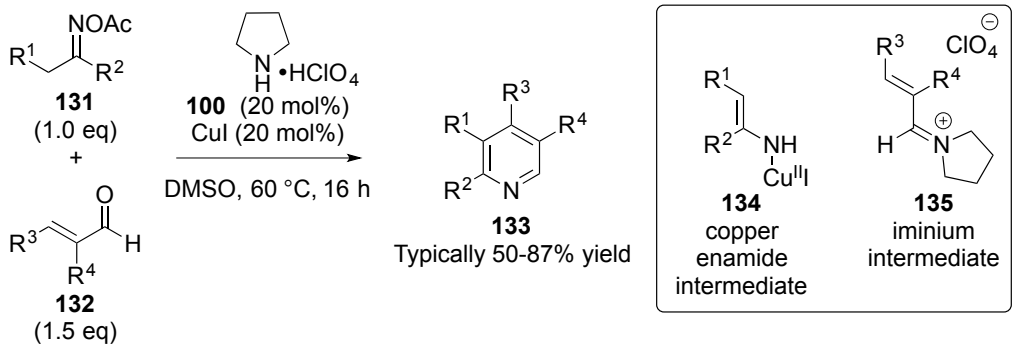


b.) Wang and co-workers - 2015.



Scheme 27 - Application of enamides towards pyridine synthesis by a.) Movassaghi, 2007 and b.) Wang, 2015.

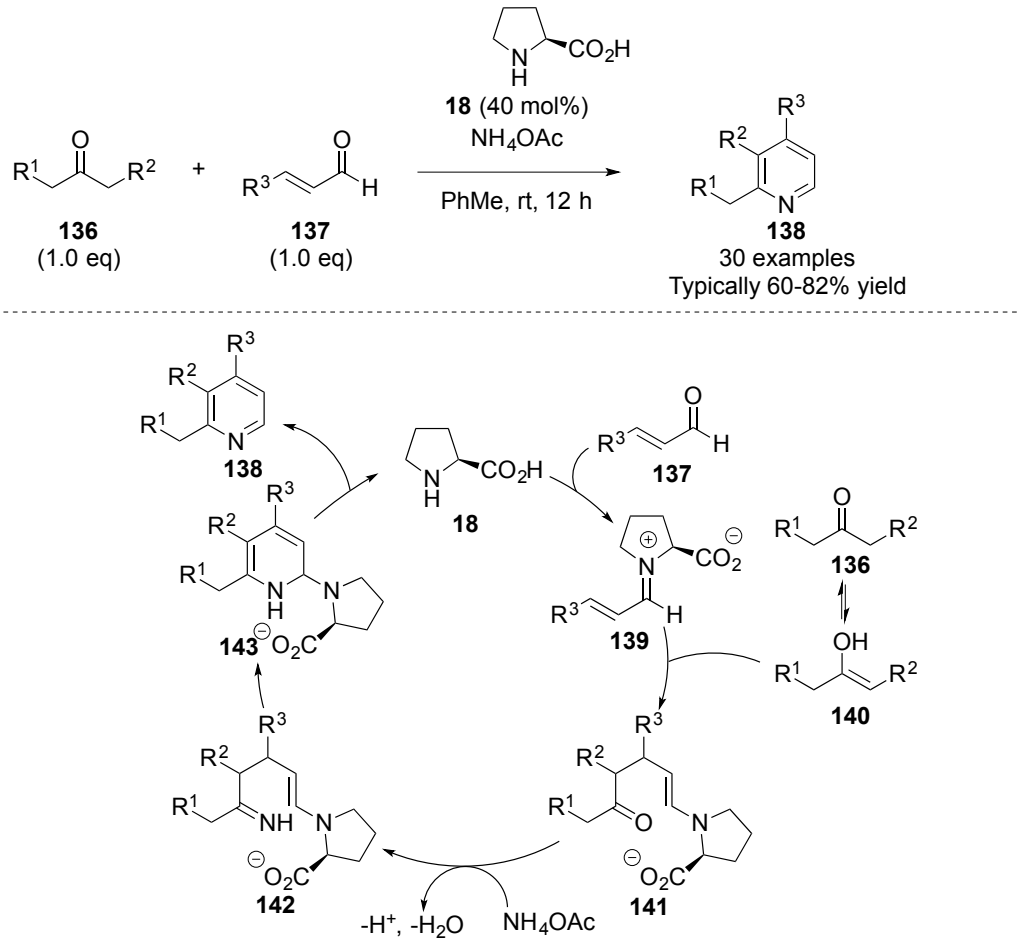
Despite the dominance of metal-catalysed processes, an initial endeavor to apply organocatalytic reactivity modes towards pyridine synthesis was the synergistic protocol by Yoshikai and co-workers reported in 2013.[66] Reduction of oxime **131** with Cu(I)I generates copper enamide intermediate **134**; simultaneously, iminium intermediate **135** is formed from enal **132** and pyrrolidine catalyst **100**. Once formed, these reactive intermediates can undergo a Michael addition/cyclisation/Cu(II)-mediated oxidation cascade to provide pyridine **133** in good yield (Scheme 28).



Scheme 28 - Synergistic iminium and copper catalysis.

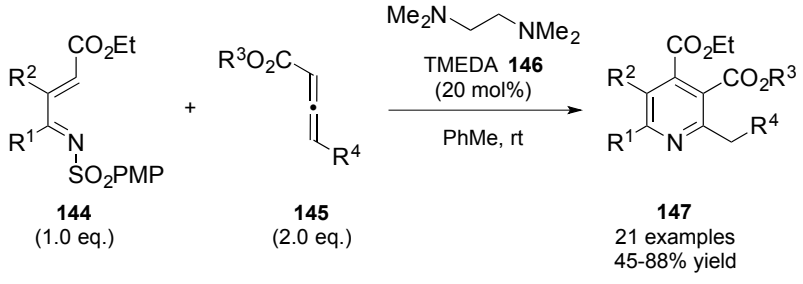
Lee and co-workers have taken inspiration from the work by Yoshikai and advanced this strategy to a solely organcatalytic procedure (Scheme 29).[67] Iminium ion **139**, generated from the condensation of enals **137** with catalytic proline **18**, is attacked by the enol form of **140** giving alkylated intermediated **141**. Reaction with ammonium acetate gives imine **142** that undergoes proton migration and subsequent intramolecular cyclisation into **143**. Pyridine **138** is formed from oxidative aromatisation and regenerates the proline catalyst **18**. Yields are

generally good for many examples bearing aryl groups at R^2 and R^3, and show excellent regioselectivity in the cases where $R^1 \neq R^2$.



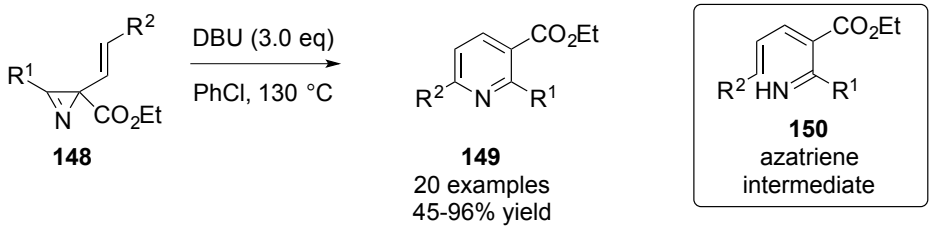
Scheme 29 - Organocatalysed oxidative *N*-annulation for the synthesis of pyridines and proposed mechanism.

Only recently have metal-free and organocatalytic methods emerged as serious competition for the more developed transition metal-catalysed processes. A notable example was reported in 2013 by Loh and co-workers who presented an aza-Rauhut-Currier/cyclisation/desulfonation cascade route to functionalised pyridines (Scheme 30).[68] Treatment of allenoate **145** with ketimine **144** in the presence of catalytic, commercially available, TMEDA **146** provides a one-pot cascade to 2,3,4,6-substituted pyridines **147** in excellent yield (up to 88%).



Scheme 30 - Aza-Rauhut/cyclisation/desulfonation cascade route to pyridines.

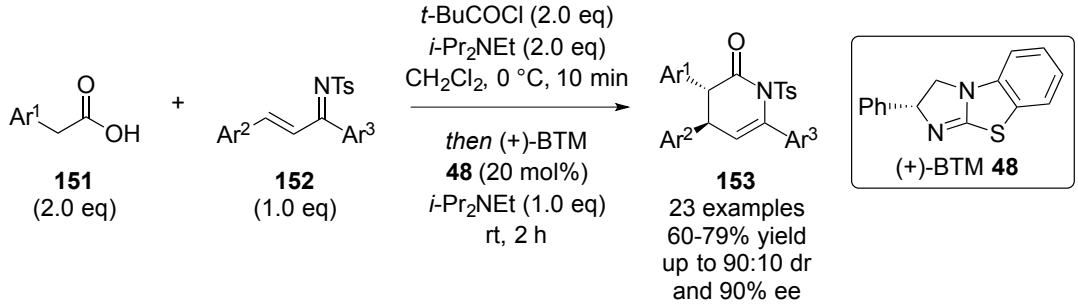
In 2014 Loh expanded his pyridine work with a protocol based on the ring expansion of 2-allyl 2*H*-azirines.[69] Treatment of azirine **148** with DBU opens the ring to generate azatriene intermediate **150**, that at the elevated temperature of 130 °C undergoes a 6π–electrocyclisation and oxidation to provide pyridines **149** (Scheme 31). Overall, the pyridine yields are good to excellent for this process however the multiple steps required to synthesise the azirine substrates may limit applications of this methodology.



Scheme 31 - Metal-free synthesis of pyridines from 2-allyl 2*H*-aziridines.

2.2 Initial Discovery of Isothiourea Catalysed Pyridine Synthesis

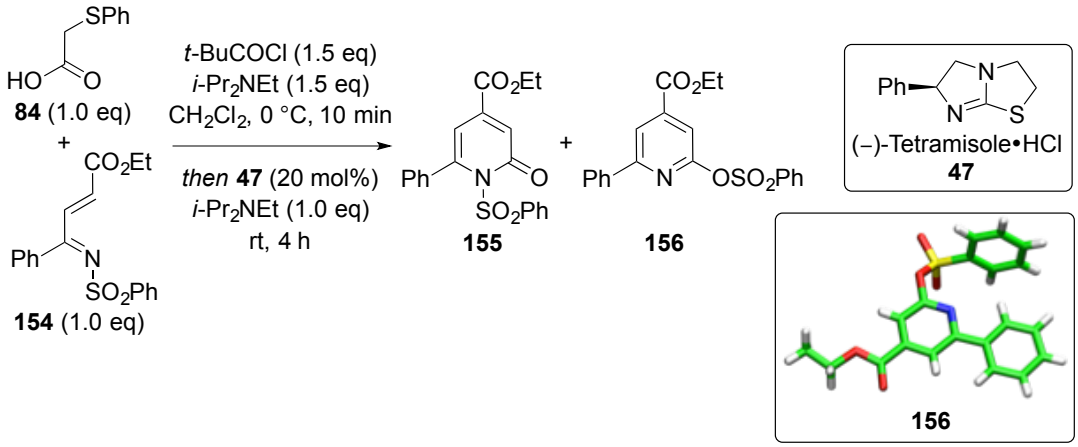
Nitrogen containing heterocycles have been prepared previously in the Smith group *via* isothiourea-catalysed intermolecular Michael addition-cyclisation protocols.[70] In 2012 Smith and co-workers reported the synthesis of *anti*-dihydropyridinones **153** in high yield, dr and ee using chalcone derived α,β-unsaturated ketimines **152** and aryl acetic acids **151**, catalysed by benzotetramisole (+)-(BTM) **48** (Scheme 32). This builds upon the Smith group's work on the use of carboxylic acids as ammonium enolate precursors in Lewis base catalysis, through the use of pivaloyl chloride and *i*-Pr_2NEt to produce a mixed anhydride *in situ* that can then be intercepted by a Lewis base catalyst.



Scheme 32 - Isothiourea-catalysed Michael addition-lactamisation.

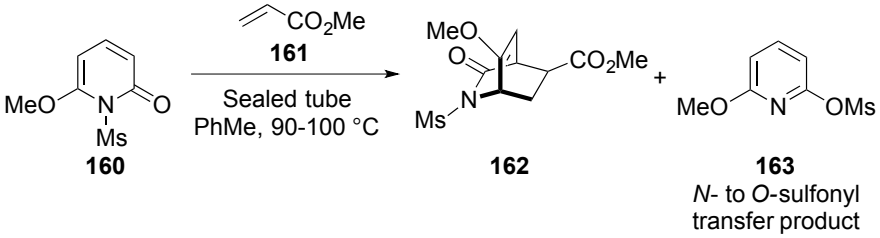
Following this, the Smith group extended the scope of accessible dihydropyridinones by applying β-ester-α,β-unsaturated ketimines **154** in the methodology.[44] Application of these Michael acceptors proved successful, however the reaction of (phenylthio)acetic acid **84** gave an undesired elimination of PhSH to yield a mixture of pyridone **155** and pyridine **156** (≈50:50). A small portion of **156** could be isolated and the constitution confirmed by X-ray crystallography to be that of pyridine **156**. Following the Michael addition-lactamisation process it can be assumed that the intermediate dihydropyridinone undergoes elimination of

PhSH to yield **155** with some pyridone undertaking a further isomerisation to pyridine sulfonate **156**. [71]



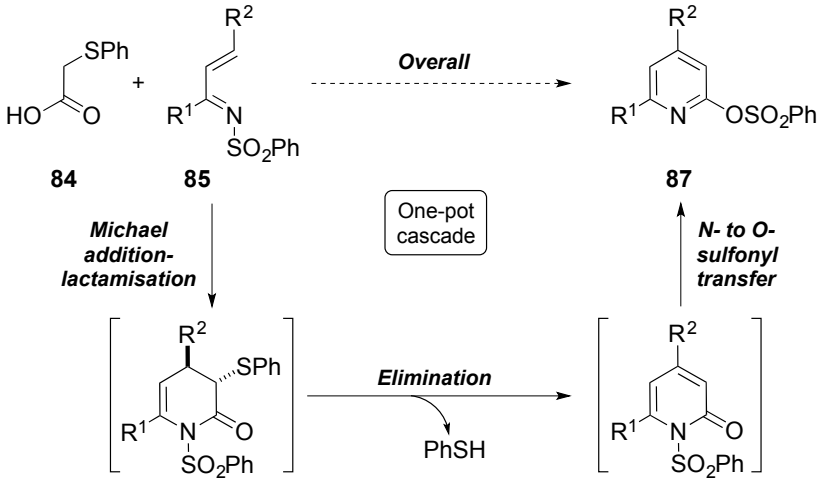
Scheme 33 - Previously observed formation of pyridine sulfonate 156 (P.-P. Yeh, Smith Group).

It was anticipated that this observation could be optimised to provide a concise route to functionalised aromatic heterocycles. Particularly the presence of the *N*- to *O*-sulfonyl transfer step would present a succinct and efficient route into substituted pyridine sulfonates, with the attractive feature of introducing a useful functional handle for further elaboration. This appealing *N*- to *O*-sulfonyl transfer process has been reported sporadically over the past few decades, although to date this isomerisation is traditionally considered as an undesirable side-product. For example Mahmood and Afarinkia reported in 1998 that the desired Diels-Alder reaction between pyridone **160** and olefin **161** gave a ratio of the expected adduct **162** and the corresponding pyridine mesylate **163** arising from *N*- to *O*-sulfonyl transfer (Scheme 34).



Scheme 34 - Literature precedent for *N*- to *O*-sulfonyl transfer.

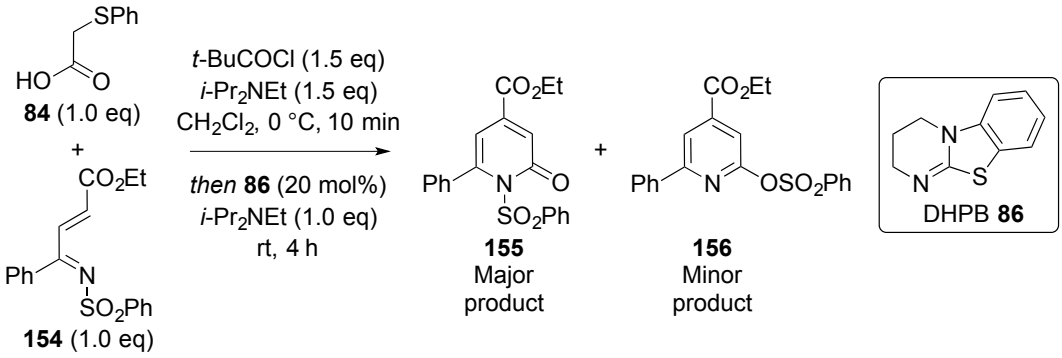
Building upon these results, the aim of this project, therefore, was to exploit these observations and optimise an isothiourea-catalysed Michael addition-lactamisation/PhSH elimination/*N*- to *O*-sulfonyl transfer one-pot cascade, towards functionalised pyridine synthesis (Scheme 35).



Scheme 35 - Proposed isothiourea-mediated route to functionalised pyridines.

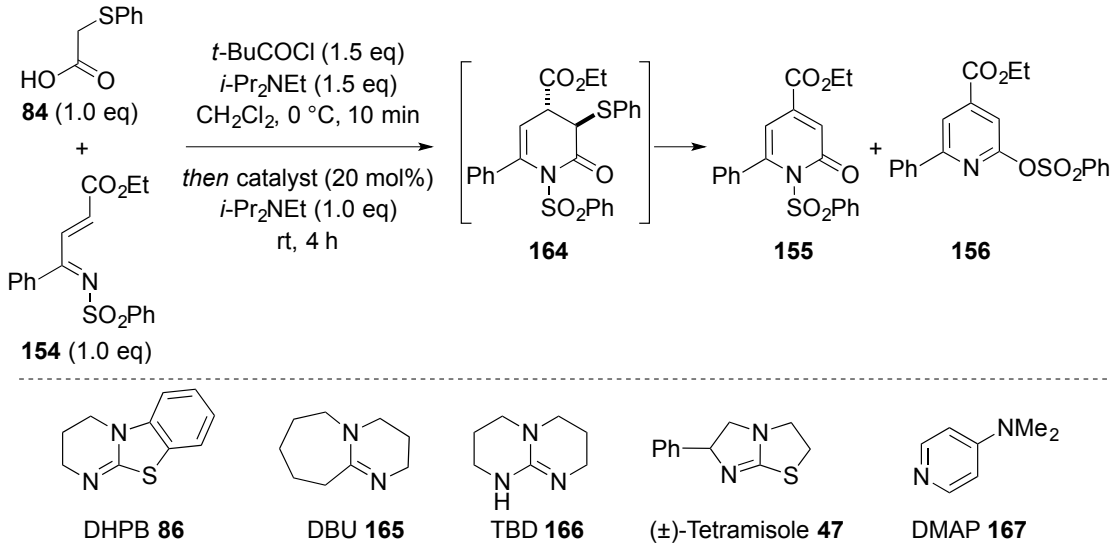
2.3 Reaction Optimisation

Firstly, the reaction described above was repeated with achiral isothiourea DHPB **86** as the catalyst (Scheme 36). Full consumption of ketimine **154** was observed after 4 h providing a 4:1 mixture of the pyridone **155** and the desired pyridine **156** (**155**:**156**) as determined by ^{1}H NMR analysis. **155** and **156** were not separable by column chromatography and could therefore not be fully characterised at this point.



Scheme 36 - Initial result.

Optimisation of this process was initiated to selectively favour the synthesis of the desired pyridine products. As no stereoinduction was required in this reaction, a range of commercially available achiral and racemic Lewis base catalysts were screened (Table 1). This catalyst screen found that DHPB **86** provided **156** in the highest yield (30%). Typically reactions with **47** and **167** gave a mixture of dihydropyridinone **164**, pyridone **155** and decomposition material. In all cases no ketimine **154** was observed by ^{1}H NMR spectroscopic analysis after 4 h.



Entry	Catalyst	Yield (%)[a]	Ratio (155:156)[b]
1	86	30	4:1
2	165	13	5:1
3	166	4	7:1
4	47	–[c]	–[c]
5	167	–[c]	–[c]

[a]Isolated yield following column chromatography. [b]Determined by ^{1}H NMR analysis.

[c]Did not yield **156**

Table 1 - Reaction optimisation: Lewis base catalyst screen.

The key observation from this initial study was the higher ratio of pyridone **155** compared with pyridine **156** present in the crude mixture. This was apparent from the ^{1}H NMR spectroscopic analysis of the crude mixture with pyridone C(3)*H* and C(5)*H* signals present at 6.65 and 6.96 ppm, respectively (Figure 19). Additionally, the distinct ^{1}H NMR signals for the ester C*H*$_2$ of pyridone **155** and pyridine **156** provided a good guide for the **155**:**156** ratio and hence an indication for the extent of the cascade process. Ratios were typically in the region of 4:1-7:1 (pyridone:pyridine) for entries 1-3 (Table 1). From these results two main deductions were made (i) elimination **164** into **155** proceeds quickly, with observation of **164** difficult to obtain by TLC analysis in many cases (ii) the poor ratio of **155**:**156** shows the *N*- to *O*-sulfonyl transfer to be sluggish under the reaction conditions.

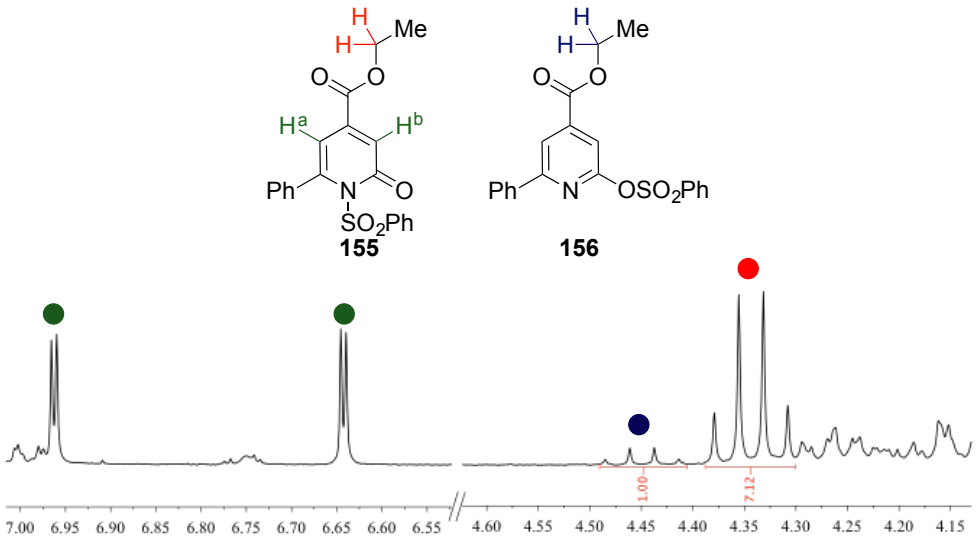
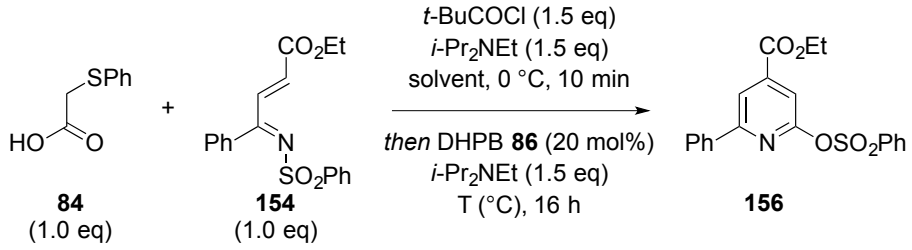


Figure 19 - Typical ^{1}H NMR spectra of a crude reaction mixture(4.15-4.6 and 6.55-7.00 ppm shown).

DHPB **86** (20 mol%) was carried forward as the optimum catalyst with the focus on driving the reaction from pyridone **155** through to pyridine **156**. Varying the reaction time and temperature were next investigated (Table 2). Longer reaction times at rt was not beneficial with a time of 24 h giving only 8% isolated yield of **156** and 168 h giving no observable **156**. The reactions were able to reach intermediate dihydropyridinone **164** and pyridone **155** (evaluated by ^{1}H NMR spectroscopic analysis) but, over the increased reaction time period these intermediate species degraded before being converted into **156**. Decreasing the reaction temperature to 0 °C and −78 °C in an attempt to minimise decomposition gave poor conversion into **156** at 0 °C and no observable **156** at −78 °C. Increasing the temperature to 40 °C and 60 °C did not provide any significant improvement over that of the reaction at rt. Gratifyingly, at the elevated temperature of 80 °C in THF in a screw-top vial, ^{1}H NMR spectroscopic analysis of the crude mixture indicated only trace pyridone **155** and what appeared to be less degradation than observed previously. This made isolation of **156** *via* column chromatography considerably easier. Further experimentation showed that allowing the initial Michael addition-lactamisation and elimination to occur at rt over 4 h followed by heating to 80 °C for 16 h led to a much improved 67% isolated yield of pyridine **156** with no pyridone **155** observed in the crude reaction mixture. It is logical to assume that the increased temperature aids the final *N*- to *O*-sulfonyl transfer step, thus being driven by the formation of the thermodynamically favourable pyridine product. This result also correlates with the literature reports of this process, with elevated reaction temperatures affording higher conversion into the isomerisation product. Analysis of the crude mixture by ^{1}H NMR spectroscopy from the reaction at 80 °C showed the desired pyridine **156** in addition to some decomposition, which accounted for the remainder of the theoretical yield.



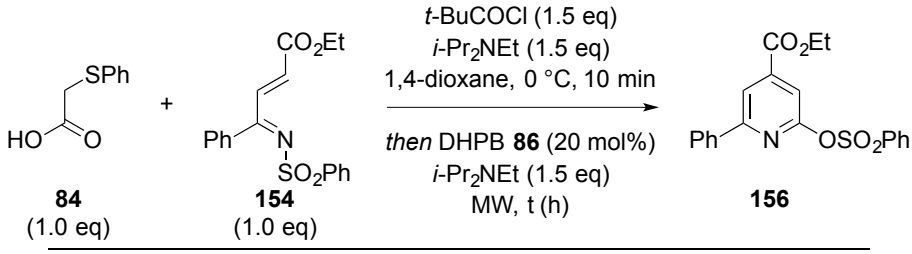
84 (1.0 eq) **154** (1.0 eq) **156**

Entry	Solvent	T (°C)	Yield (%)[a]	Ratio (155:156)[b]
1	CH_2Cl_2	−78	–[c]	–[c]
2	CH_2Cl_2	0	7	7:1
3	CH_2Cl_2	rt	30	4:1
4	THF	40	–[d]	1:1
5	THF	60	–[d]	1:1
6	THF	rt-80	67	–[e]
7	THF[f]	80	10	4:1
8	THF	120	35	2:1

[a]Isolated yield following column chromatography.. [b]Determined by ^{1}H NMR analysis. [c]Did not yield **156**. [d]Not pursued further. [e]No pyridone observed. [f][0.06 M] (typically [0.6 M].

Table 2 - Reaction optimisation: solvent and temperature screen.

In an attempt to assist the *N*- to *O*-sulfonyl transfer a microwave reactor was investigated as an alternative energy source (Table 3). A Biotage Initiator with a program of heating to 80 °C at 150 W using low absorption settings was used for this. Two reactions were conducted at different reaction times of 1 h and 4 h in 1,4-dioxane (recommended as the optimum solvent for this instrument). Both reactions produced promising results with **156** isolated in 45% and 52% yield for 1 h and 4 h reaction, respectively. However, as the microwave heating source showed no significant advantage over the conventional heating methods this option was not pursued any further.



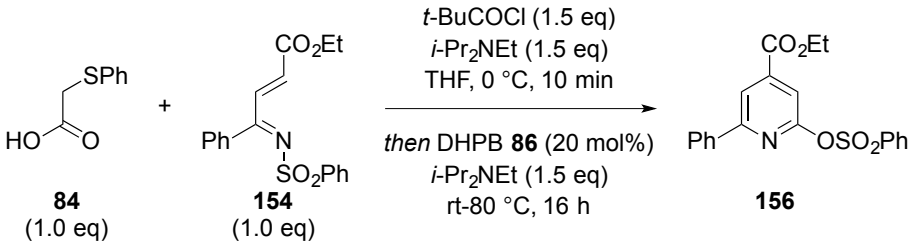
84 (1.0 eq) **154** (1.0 eq) **156**

Entry	MW reaction time (h)	Yield (%)[a]
1	1	45
2	4	52

[a]Isolated yield following column chromatography. MW = Biotage Initiator with a program of heating to 80 °C at 150 W using low absorption settings.

Table 3. - Microwave-assisted reaction.

Next a catalyst loading screen was conducted (Table 4). The reaction tolerates catalyst loadings down to 1 mol%, however there was a significant decrease in isolated yield compared with use of 20 mol% DHPB **86**. It can be tentatively suggested that the Michael addition-lactamisation proceeds at a slower reaction rate when using lower catalyst loadings, allowing more time for ketimine **154** and other potential intermediates to decompose before conversion to products.



84 (1.0 eq) **154** (1.0 eq) **156**

Entry	Catalyst (mol%)	Yield (%)[a]
1	20	67
2	10	20
3	5	15
2	1	10

[a]Isolated yield following column chromatography.

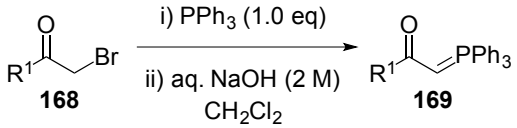
Table 4 - Reaction optmisation: catalyst loading screen.

2.4 Substrate Scope: Variation of β-Ester-α,β-Unsaturated Ketimines

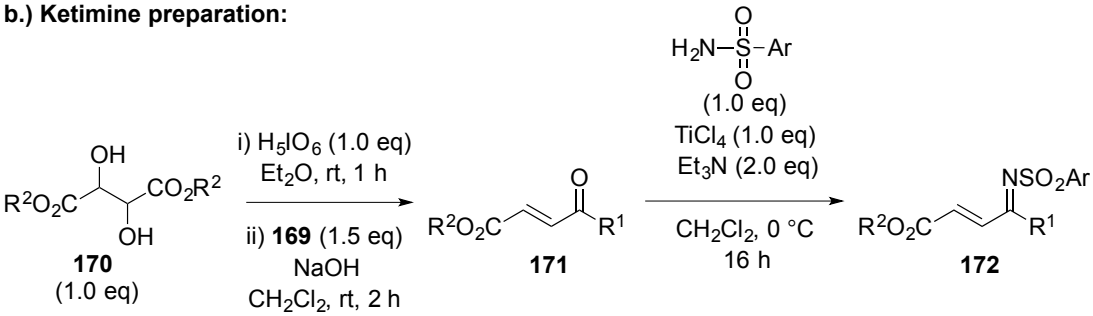
2.4.1 Synthesis of β-Ester-α,β-Unsaturated Ketimines

With the optimum conditions for the isothiourea-catalysed Michael addition-lactamisation/PhSH elimination/*N*- to *O*-sulfonyl transfer cascade in hand the generality of this protocol was investigated. To extend the scope beyond the parent Michael acceptor, a range of β-ester-α,β-unsaturated ketimines was prepared from the corresponding γ-keto-α,β-unsaturated esters. Employing the synthesis from Lu and co-workers, phosphoranes **169** were prepared from the corresponding α-bromo ketones **168** (Table 5a).[72] Next the requisite glyoxylates were prepared *in situ* from an oxidative cleavage of the corresponding tartrate **170** with periodic acid. Treatment of these glyoxylate intermediates with phosphoranes **169** in a Wittig reaction gave keto esters **171**. Treatment of keto ester **171** with the requisite sulfonamide in the presence of $TiCl_4$ and Et_3N affords β-ester-α,β-unsaturated ketimines **172** (Table 5b). Keto esters **173-178** were obtained in typically good yield whereas the ketimines **179-184** proved challenging to purify and in most cases were used as crude mixtures of 80-90% purity (as determined by ^1H NMR spectroscopic analysis). Additional substrates applied in the substrate scope were available within the Smith Group.[73]

a.) Phosphorane preparation:



b.) Ketimine preparation:



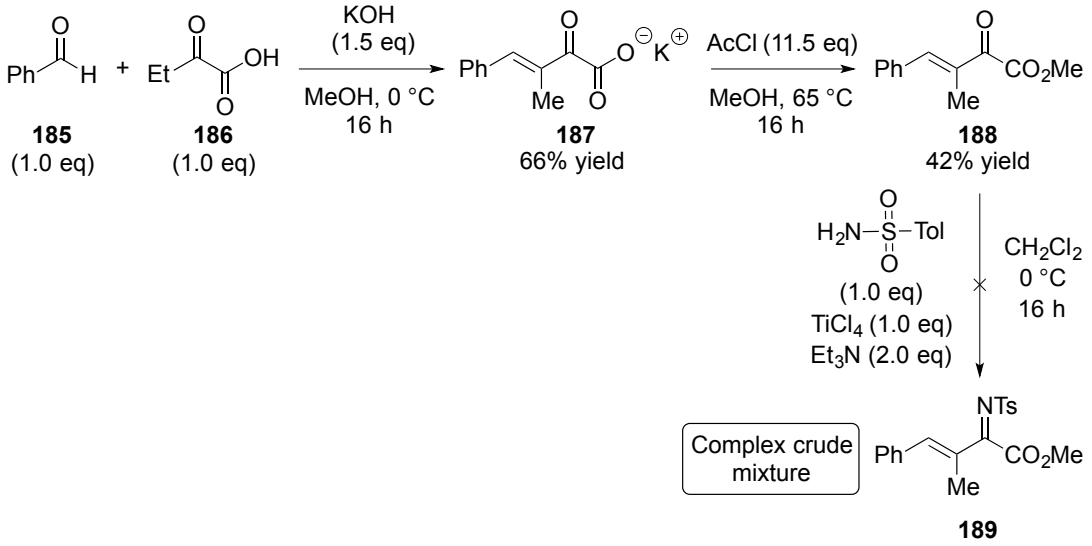
Keto ester					Ketimine				
Entry	**No.**	**R^1**	**R^2**	**Yield (%)[a]**	**Entry**	**No.**	**R^1**	**R^2**	**Yield (%)[a]**
1	**173**	Ph	Et	–[b]	**7**	**179**	Ph	Et	45[c]
2	**174**	Ph	Me	64	**8**	**180**	Ph	Me	–[d]
3	**175**	4-CNC_6H_4	Me	59	**9**	**181**	4-CNC_6H_4	Me	–[d]
4	**176**	4-$CF_3C_6H_4$	Me	90	**10**	**182**	4-$CF_3C_6H_4$	Me	–[d]
5	**177**	2-Np	Me	81	**11**	**183**	2-Np	Me	–[d]
6	**178**	*t*-Bu	Me	85	**12**	**184**	*t*-Bu	Me	34[c]

[a]Isolated yield following column chromatography. [b]Purchased from commercial source. [c]Isolated following recrystallisation. [d]Obtained as a crude mixture.

Table 5 - a.) Preparation of phosphoranes. b.) Synthesis of β-ester α,β-unsaturated ketimines.

c.) Results table.

To allow application of the methodology to the synthesis of 2,4,5,6-substituted pyridines the synthesis of the tri-substituted ketimine **189**, with the additional Me substituent at the β-position, was attempted. Applying modified procedures from Srivastava[74] and Zhang[75] for the preparation of γ-aryl-β,γ-unsaturated α-ketoesters, the route began with an aldol reaction between benzaldehyde **185** and 2-ketobutyric acid **186** with potassium hydroxide, providing potassium carboxylate salt **187** in 66% yield (Scheme 37). Treatment of **187** with methanol and acetyl chloride gives the ketoester **186** in 42% yield. Unfortunately, condensation with 4-toluenesulfonamide was unsuccessful and complex crude reaction mixture was obtained from which ketimine **189** could not be isolated.



Scheme 37 - Attempted synthesis of ketimine 189.

2.4.2 Reactivity of β-Ester-α,β-Unsaturated Ketimines

Investigation into the generality of the isothiourea-catalysed pyridine formation was initiated with variation of the ester substituents within the ketimine (Table 6). Methyl and ethyl esters are accommodated giving pyridines **190** and **191** in good 60% and 67% yield, respectively. Benzyl ester groups could also be incorporated with the corresponding pyridine **192** obtained in moderate 50% yield over the three-step cascade.

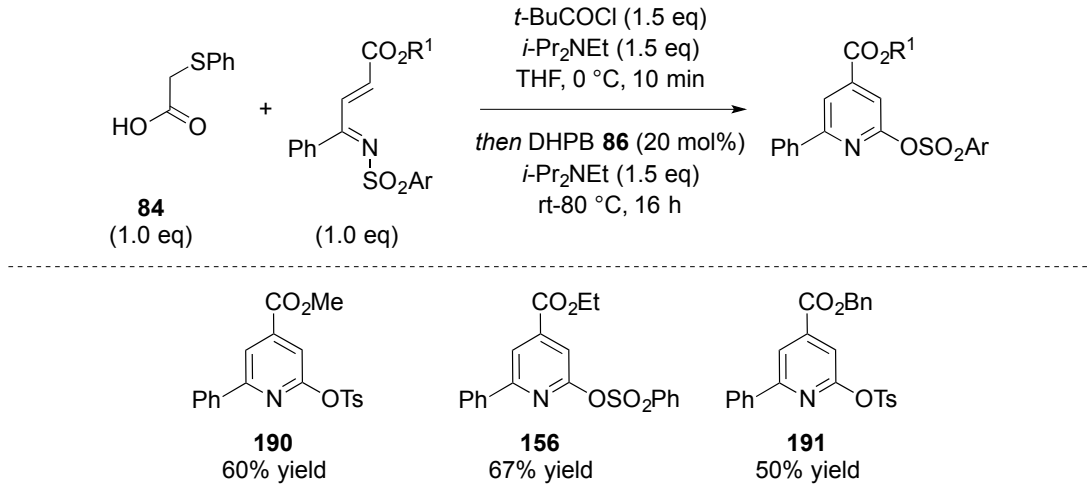


Table 6 - Substrate scope: variation of ester substituent.

The broad range of unsaturated ketimines synthesised bearing various groups at the C(1) position were next subjected to the previously optimised reaction conditions (Table 7). The 2-Np substituent could be installed into the product giving pyridine **192** in excellent 69% yield. Electron-rich 4-MeC_6H_4 and 4-MeOC_6H_4 substituents are tolerated to provide the corresponding products **193** and **194** in moderate 51% and 50% yield, respectively. Further functionality could

be installed onto the pyridine scaffold with 4-ClC_6H_4 and 2-FC_6H_4 substituents being accepted providing products **195** and **196** in good yield. Electron-deficient aryl substituents were compatible with this methodology giving pyridines **198-199** in good yield (51-64% yield). Pleasingly, the procedure was not limited to aryl groups at the C(1) position of the Michael acceptor. The *t*-Bu alkyl substituent also participates with moderate reactivity, delivering pyridine **200** in a 44% isolated yield.

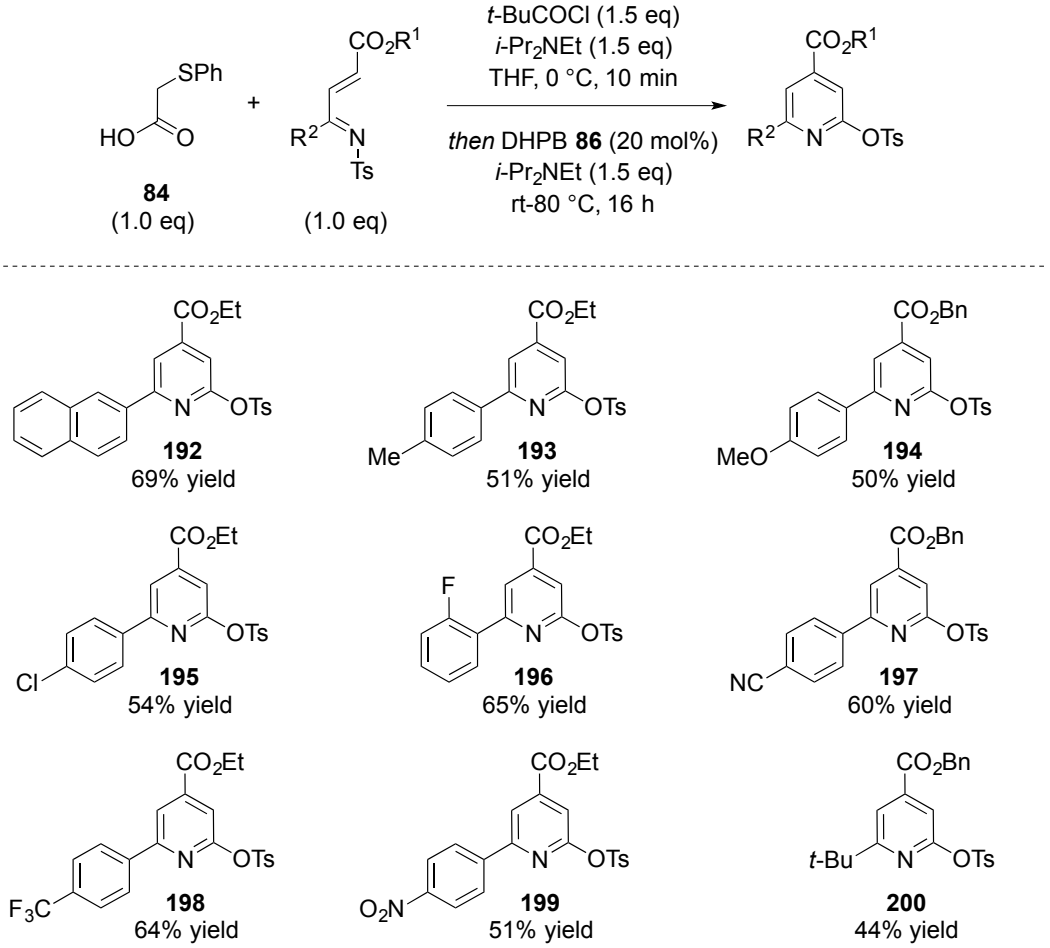


Table 7 - Substrate scope: variation of 2-substituent.

Five ketimines were recalcitrant to this protocol (Table 8). In the case of 1-Np **201** and biphenyl **202** there was no conversion to the desired pyridine product with only starting materials returned, whereas the styryl ketimine provided the product **203** with a poor 30% conversion (as determined by ^{1}H NMR spectroscopic analysis). Unfortunately, **203** could not be isolated from a complex crude mixture. The 1-Np ketimine may be too sterically demanding for the initial Michael addition step. The biphenyl and styryl results are particularly surprising, as it would be predicted that these variations in the Michael acceptors should not impart any significant electronic or steric demands to explain the lack of reactivity. To extend the scope beyond trisubstituted pyridines the α,α–disubstituted acids 2-(phenylthio)propanoic acid and 3-

methyl-2-(phenylthio)butanoic acid were examined. Unfortunately, the intended tetrasubstituted pyridines **204** and **205** were not formed, with the starting materials returned.

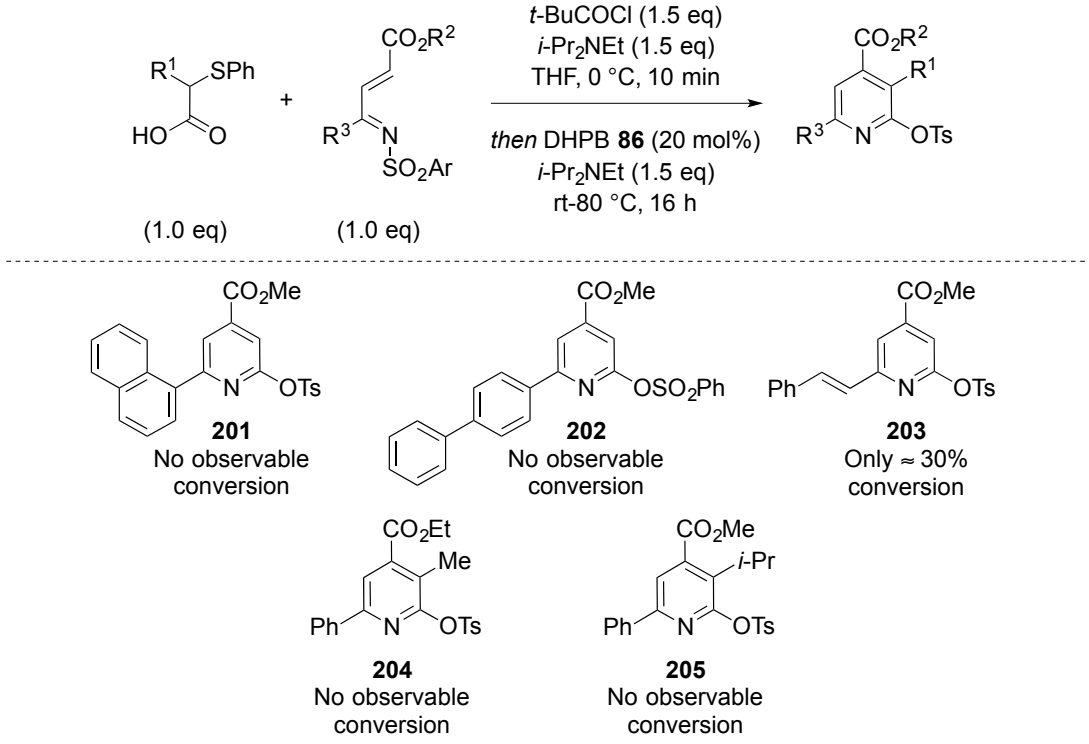


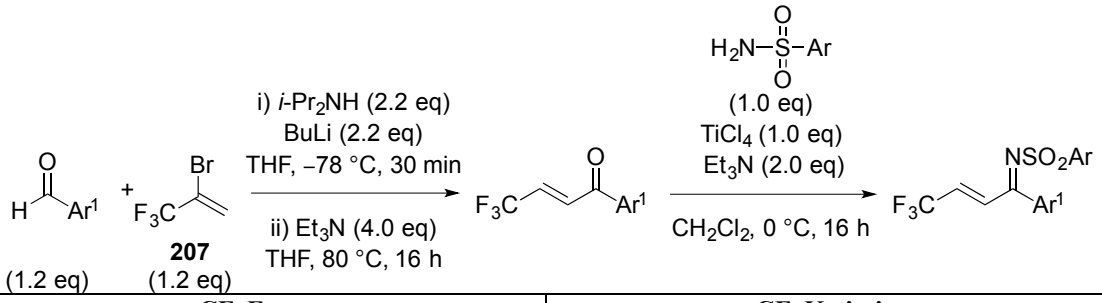
Table 8 - Unsuccessful 4-ester pyridine results.

2.5 Substrate Scope: Variation of β-Trifluoromethyl-α,β-Unsaturated Ketimines

2.5.1 Synthesis of β-Trifluoromethyl-α,β-Unsaturated Ketimines

In recent decades, the inclusion of trifluoromethyl groups within drug-like molecules has become highly appealing due to the potential impact these substituents may have upon that compounds biological activity.[76] Based on this interest, further work looked to extend this methodology to access pyridines containing the important trifluoromethyl functional group. Firstly, a series of trifluoromethyl ketimine substrates were synthesised (Table 9). Following the procedure reported by Yamazaki, trifluoromethyl enones were synthesised *via* a two-step procedure. Treatment of 2-bromo-3,3,3-trifluoroprop-1-ene **207** with LDA at −78 °C and subsequent addition of arylaldehyde gave an intermediate propargyl alcohol that underwent isomerisation, in the presence of Et_3N, to yield a mixture of (*E*) and (*Z*)-enones (≈ 80:20 *E*:*Z* ratio in all cases). Isolation of the (*E*)-enone and subsequent condensation with 4-toluenesulfonamide in the presence of $TiCl_4$ and Et_3N gave α,β-unsaturated ketimines **214**-**220**. Generally, the trifluoromethyl ketimines proved easier to isolate than the ester variants

mentioned previously with all compounds being crystalline solids that were recrystallised from Et_2O.



CF_3 Enones				CF_3 Ketimines			
Entry	**No.**	**Ar^1**	**Yield (%)[a]**	**Entry**	**No.**	**Ar^1**	**Yield (%)[b]**
1	**207**	2-BrC_6H_4	40	**9**	**215**	2-BrC_6H_4	50[a]
2	**208**	3-BrC_6H_4	45	**10**	**216**	3-BrC_6H_4	80
3	**209**	4-BrC_6H_4	66	**11**	**217**	4-BrC_6H_4	68
4	**210**	4-MeC_6H_4	42	**12**	**218**	4-MeC_6H_4	70
5	**211**	4-FC_6H_4	35	**13**	**219**	4-FC_6H_4	62
6	**212**	2-Np	59	**14**	**220**	2-Np	61
7	**213**	2-Thienyl	27	**15**	**221**	2-Thienyl	80
8	**214**	2-Pyridyl	–[c]				

[a]Isolated following column chromatography. [b]Isolated following recrystallisation. [c]Did not provide product.

Table 9 - Synthesis of β-trifluoromethyl-α,β-unsaturated ketimines

2.5.2 Reactivity of β-Trifluoromethyl-α,β-Unsaturated Ketimines

With a selection of trifluoromethyl ketimine Michael acceptors in hand, their reactivity in the previously optimised one-pot pyridine cascade was assessed (Table 10). 4-BrC_6H_4 substituents are well tolerated with the possibility for placing the bromo-substituent at either the 3- or 4-position of the ring to give pyridines **221** and **222** in 60% and 52% yield, respectively. These examples provide a further functional handle within the molecule for potential derivatisation. However, the 2-BrC_6H_4 ketimine **214** did not show any conversion into the desired pyridine **223**. It is likely the presence of the 2-Br substituent is too sterically demanding for the approach of the ammonium enolate towards the Michael acceptor. Electron-rich substituent 4-MeC_6H_4 was included in the resulting pyridine **224** obtained in good 60% isolated yield. The 4-FC_6H_4 substituent can be incorporated at the 6-position of the product giving pyridine **225** in a moderate 45% yield. Full consumption of the 4-FC_6H_4 ketimine was observed by ^{1}H NMR spectroscopic analysis, implying that the ketimine may have been too unstable, resulting in decomposition under the reaction conditions. In the case of the 2-Np **226** and 2-thienyl **227** examples around 60% conversion (detected by ^{1}H NMR spectroscopic analysis) was

observed in both instances leading to moderate isolated yields (46% and 45%, respectively). These results imply low reactivity between the corresponding trifluoromethyl ketimines towards the intermediate ammonium enolate.

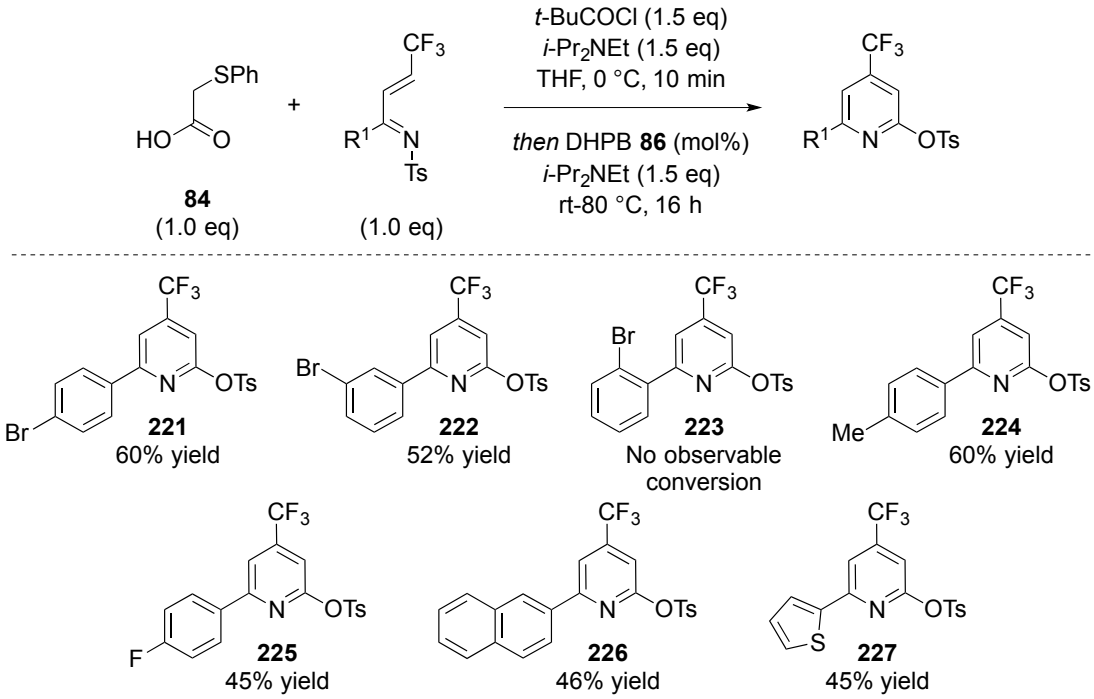
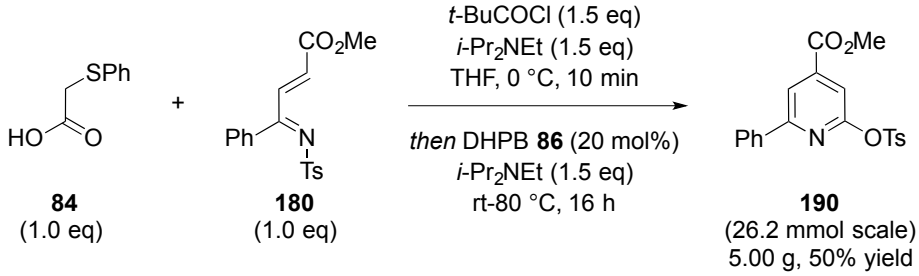


Table 10 - Scope of trifluoromethyl pyridines.

2.6 Scale-up and Derivatisation

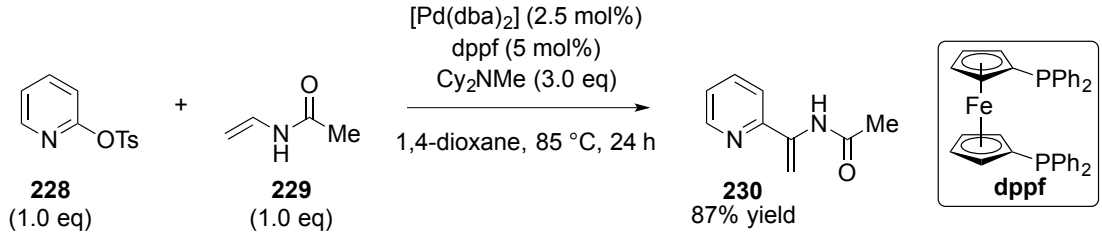
With powerful methodologies available to transform aryl functional handles, the integration of such functional groups can allow the rapid assembly of larger, more complex molecules. Pyridine **190** was prepared on a large scale (26.2 mmol scale producing 5.00 g of product) to allow investigation into the use of the tosylate functional handle as a means for derivatisation (Scheme 38).



Scheme 38 - Scaled-up synthesis of 190.

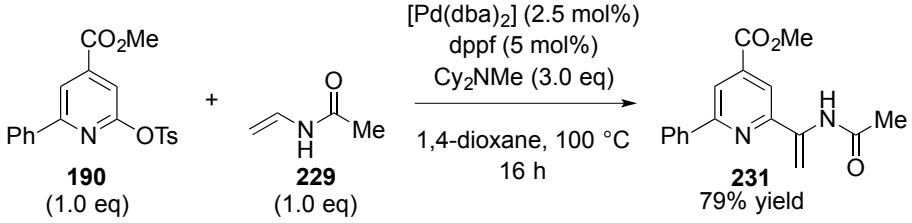
Heteroaromatic substituent modification has become key in the construction of relevant complex target molecules. This trend has been driven by the advances in highly powerful cross-coupling methods.[77] As a representative example, Skrydstrup and co-workers have shown that 2-pyridyl tosylates can easily be coupled to olefins *via* Mizoroki-Heck-coupling (Scheme

39).[78] 2-Pyridyl tosylates **228** and *N*-vinyl acetamide **229** under Mizoroki-Heck-coupling conditions yields transformed pyridine **230** in generally good to excellent yields.



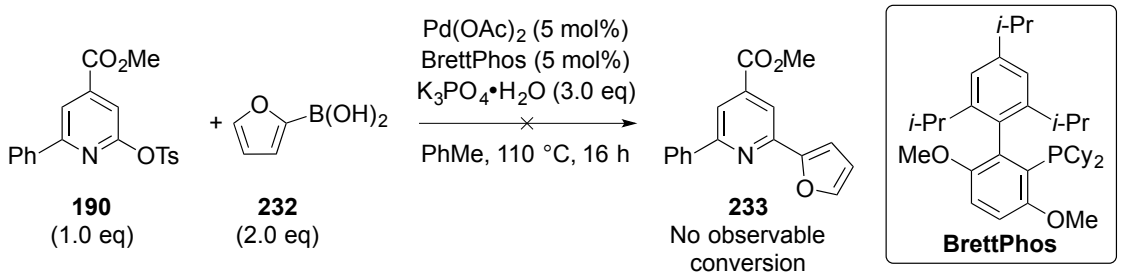
Scheme 39 - Functionalisation of pyridine tosylates by Skrydstrup.

Applying the procedure from Skrydstrup and co-workers a Mizoroki-Heck-coupling was attempted (Scheme 40).[78] $Pd(dba)_2$ (2.5 mol%), *N*-methyldicyclohexylamine (dppf, 5 mol%), *N*-vinylacetamide **229**, pyridine **190** and Cy_2NMe gave α-substituted vinyl acetamido pyridine **231** in excellent 79% yield with no β-substituted product observed. This regioselectivity is consistent with electron-rich olefins applied in the Mizoroki-Heck reaction under these conditions.



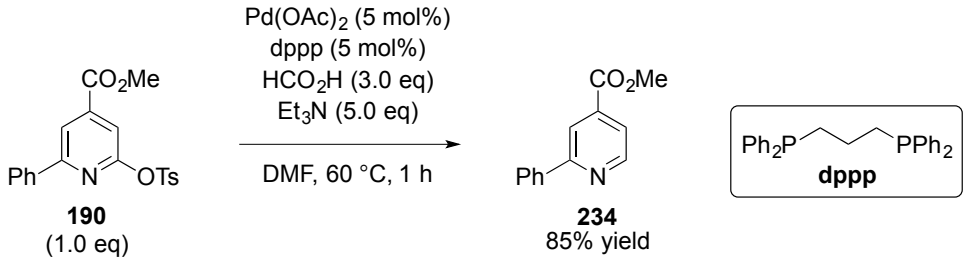
Scheme 40 - Mizoroki-Heck reaction on pyridine 190.

Using the procedure from Buchwald, pyridine **190** was treated under Suzuki-Miyaura coupling conditions using $Pd(OAc)_2$ (5 mol%), BrettPhos (5 mol%) and $K_3PO_4 \bullet H_2O$ in PhMe at 110 °C overnight (Scheme 41).[79] This reaction led to no observation of intended product **233** and returned only starting material **190** and **232** with some **232** undergoing protodeborylation to furan. Many of the reactions, similar to this, in the literature contain pyridines without ester substituents. It may be that in this case Pd coordinates to the ester and deactivates the catalyst towards the Suzuki-Miyaura coupling at the tosylate group.



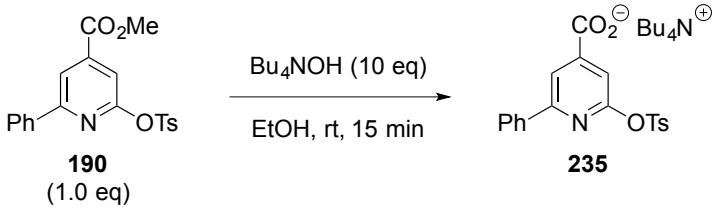
Scheme 41 - Attempted Suzuki-Miyaura coupling on pyridine 190.

The tosylate substituent can also be removed from these molecules *via* a protodetosylation to give 4,6-substituted pyridine. This was accomplished with a procedure reported from Yoshida and co-workers (Scheme 42) using $Pd(OAc)_2$ (5 mol%) and dppp (5 mol%) with formic acid to give di-substituted pyridine **235** in excellent 85% yield. [80]



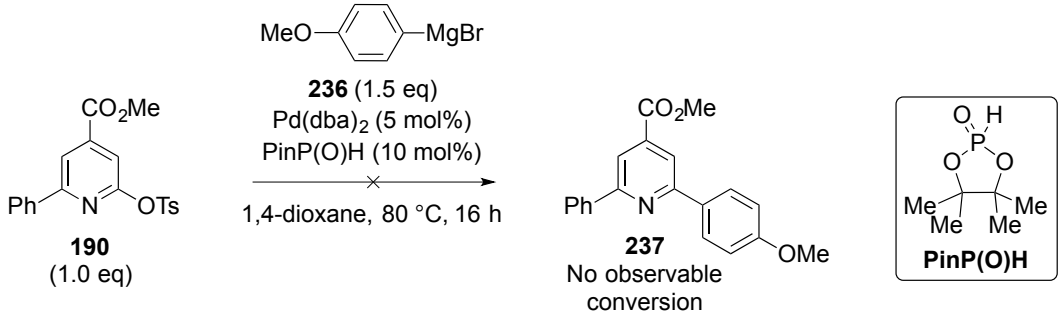
Scheme 42 - Pd-catalysed protodetosylation on pyridine 190.

An attempt to hydrolyse pyridine **190** to the corresponding 4-ester pyridone was made. However, reaction of **190** with tetrabutylammonium hydroxide resulted in hydrolysis of the ester group with no observable hydrolysis of the tosylate substituent (analysed by ^{1}H NMR spectroscopic analysis). Based on the ^{1}H NMR analysis it appeared that following hydrolysis of the ester to the carboxylate salt **235** the reaction did not proceed any further (Scheme 43).



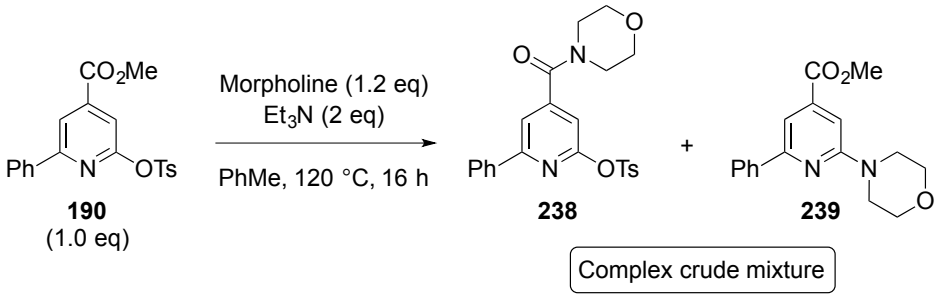
Scheme 43 - Attempted hydrolysis of 190 to corresponding pyridone.

Following the procedure by Ackermann and co-workers a Kumada cross-coupling was also attempted (Scheme 44).[81] $Pd(dba)_2$ (5 mol%) Pin(O)H (10 mol%) and 4-methoxyphenylmagnesium bromide **236** and were heated at 80 °C for 16 h. Unfortunately this gave no observable conversion (by ^{1}H NMR spectroscopic analysis) to pyridine **237**. As with the Suzuki-Miyaura reaction, the ester group may chelate to Pd and deactivate the reaction. Also surprising was that no addition of **236** into the ester group was observed.



Scheme 44 - Attempted Kumada-coupling on pyridine 190.

A nucleophilic aromatic substitution at the tosylate position using morpholine was examined (Scheme 45). This reaction gave a complex crude mixture of starting material **190**, amide **238** and desired product **239**. Efforts to separate these constituents by column chromatography proved unsuccessful.



Scheme 45 - Attempted S_NAr reaction.

Overall, derivatisation of 4-ester pyridine **190** has proven limited. This is in contrast to the 4-trifluoromethyl pyridine **240** that has been derivatised using various transformations within the Smith group (L. C. Morrill, PhD student) (Figure 20).[82]

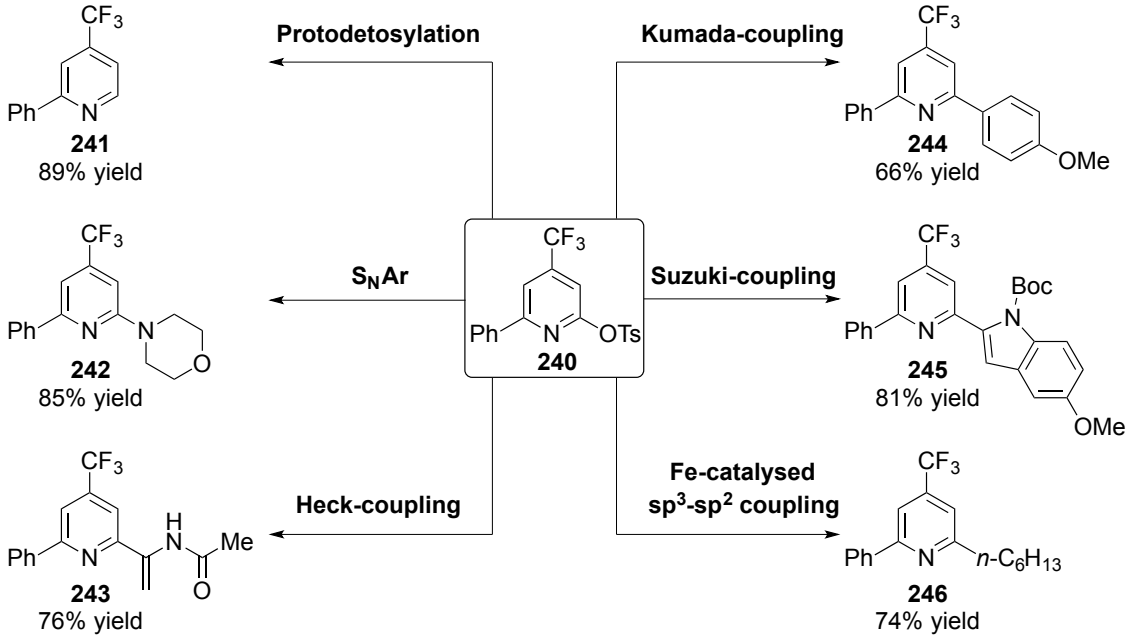


Figure 20 - Derivatisation of 4-CF_3 pyridine (L. C. Morrill, PhD student, Smith group).

2.7 Reaction Mechanism

It is proposed that the cascade process begins with *N*-acylation of DHPB **86** with *in situ* formed mixed anhydride **246** to generate the acyl ammonium intermediate **247** (Figure 21). Deprotonation forms the key ammonium enolate **248** that, in the presence of ketimine **249**, undergoes Michael addition to give a second acyl ammonium species **250**. This intermediate cyclises to provide dihydropyridinone **251** and regenerate the isothiourea catalyst. Under the reaction conditions, it is proposed that **251** eliminates PhSH to give to the corresponding

pyridone **252** that, at elevated temperature undergoes an *N*- to *O*-sulfonyl transfer to yield pyridine sulfonate **253**.

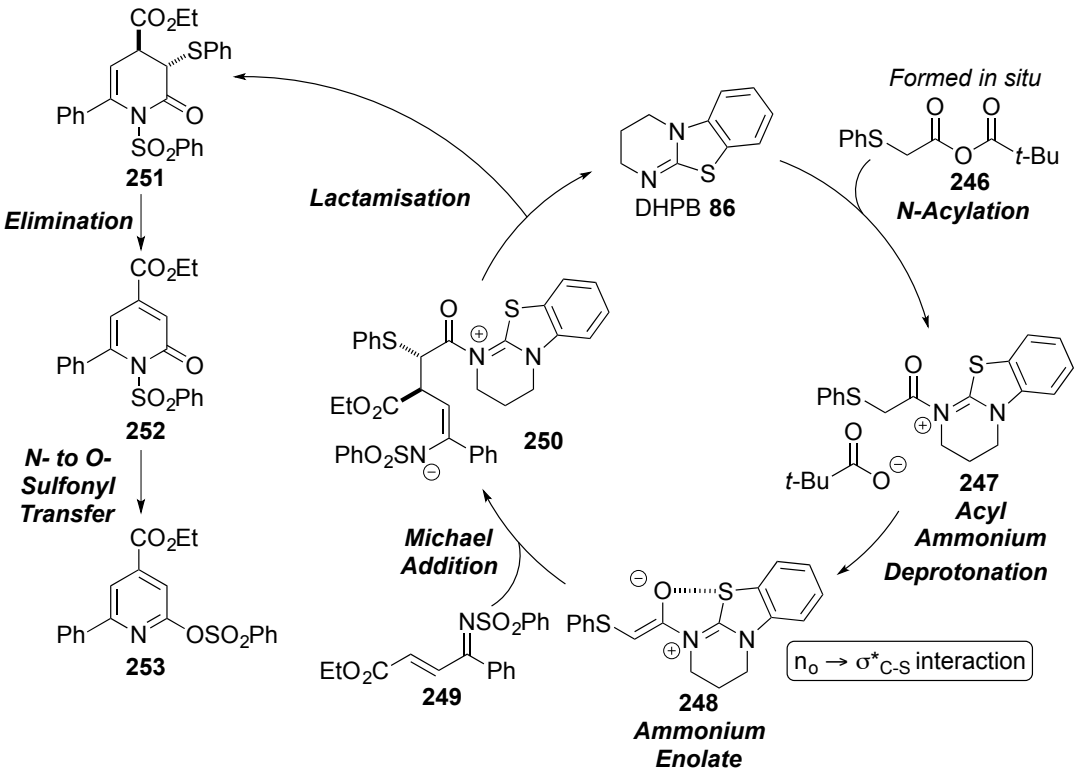


Figure 21 - Proposed mechanism for the isothiourea-catalysed Michael addition-lactamisation/PhSH elimination/ *N*- to *O*-sulfonyl transfer cascade.

Given the typically high levels of *anti*-diastereoselectivity observed in isothiourea-catalysed Michael addition-cyclisation processes the PhSH elimination becomes intriguing. In examples with ester groups installed at the C(4) position of the dihydropyridinone an E1cB mechanism is highly likely and would facilitate elimination of PhSH despite the *anti*-relative configuration at C(3) and C(4) (Figure 22).

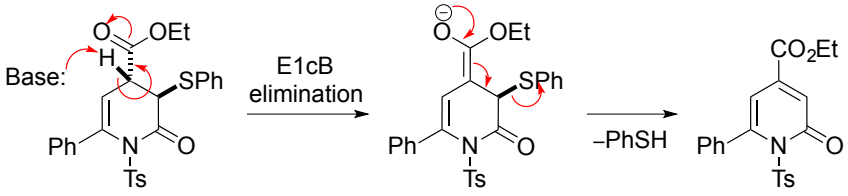


Figure 22 - E1cB mechanism for PhSH elimination.

For the cases with C(4)CF_3 substituents the mechanism for elimination is not as clear. Dihydropyridinone **254** was synthesised previously in the Smith group with the constitution and relative stereochemistry examined by X-ray crystallography (Figure 23). Although the conformation appears slightly puckered compared to a typical half-chair conformation, the stereocentres at C(3) and C(4) show the *anti*-configuration to place the protons *anti*-periplanar to one-another.

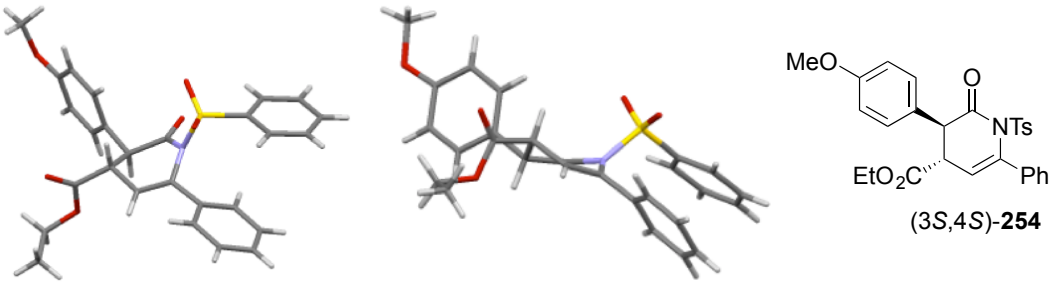


Figure 23 - Molecular representation and X-ray structure of dihydropyridinone (3*S*,4*S*)-254.

Based on this crystallographic information for (3*S*,4*S*)-**254**, it can be suggested that the *anti*-configuration at C(3) and C(4) would therefore not place the C(4) proton and –SPh leaving group *anti*-periplanar to one another and hence not provide a $\sigma_{C\text{-}H}$ to $\sigma^*_{C\text{-}S}$ orbital overlap good enough to facilitate an E2 mechanism (Figure 24). This rationale is based upon the ground state energy conformations predicted for this type of molecule however, it cannot be ruled out that at the temperature of 80 °C a high energy conformation is present and thus allows an E2-type elimination.

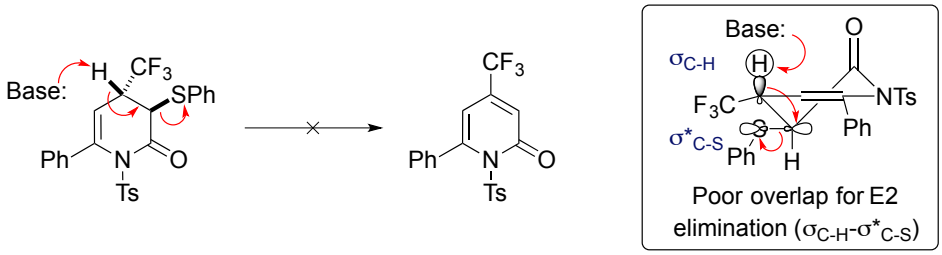


Figure 24 - Improbable E2 mechanism for elimination of PhSH.

A plausible rationalisation may be a base-promoted epimerisation at C(3) leading to a *syn*-relative configuration and therefore an orbital overlap that would be satisfactory for an E2 elimination (Figure 25). It should also be noted that oxidation of the sulfide substituent to a sulfoxide intermediate, under the reaction conditions, and a *syn*-sulfoxide elimination cannot be discounted.

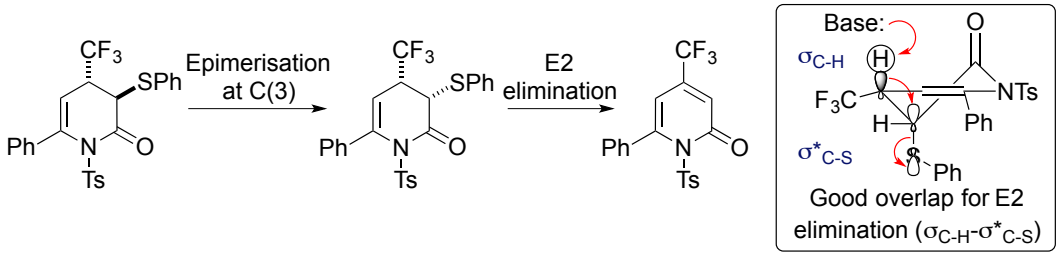


Figure 25 - Possible epimerisation at C(3) leading to an E2 elimination of the *syn*-dihydropyridinone.

To the best of our knowledge, this is the first report to apply the *N*- to *O*-sulfonyl transfer as an expedient transformation. Theoretical computational studies were explored on a model system for the conversion of pyridone **255** into pyridine **256** (Figure 26).[83],[84] Calculation of the Gibbs free energy at the M06-2X/6-31+G**/ level of theory indicates a downhill in energy of −12.1 Kcalmol^{-1}. Furthermore, the geometry-optimised structures of **255** and **256** show the conformation to change from a slightly puckered conformation in **255** to a fully planar ring system in **256**. A main characteristic of aromaticity is the planar conformation of the cyclic structure (hence leading to improved side-on interaction of the contributing p-orbitals) therefore, in addition to the observed downhill in energy, we can imply from this computational experiment that there is an increase in aromatic character and the resulting product is lower in energy. This evidence is in line with our hypothesis that the formation of the pyridine product may be a thermodynamic sink in the reaction profile and hence a potential driving force for this cascade process.

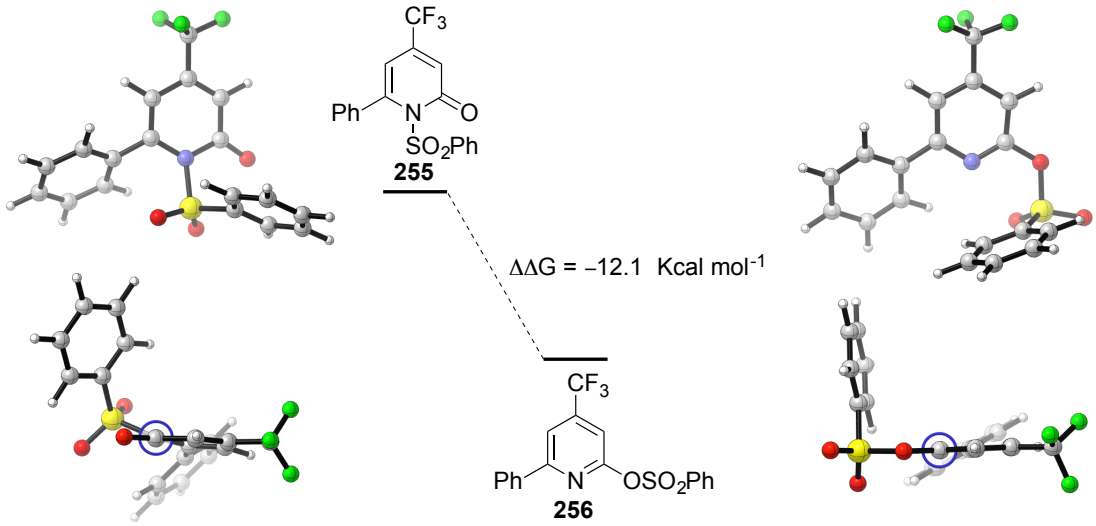


Figure 26 - *N*- to *O*-sulfonyl transfer theoretical experiment (M06-2X/6-31+G/PCM(THF)).**

2.8 Conclusions

In conclusion, isothiourea catalyst DHPB **86** mediates a three-step, one-pot cascade to produce tri-substituted pyridine sulfonates. DHPB **86** initially catalyses the Michael addition-lactamisation between (phenylthio)acetic acid and a range of trifluoromethyl- or ester-containing α,β-unsaturated ketimines in the presence of pivaloyl chloride and *i*-Pr$_2$NEt. The reaction proceeds through the elimination of PhSH to form an intermediate pyridone that, aided by elevated temperatures, undergoes an *N*- to *O*-sulfonyl transfer to provide pyridine tosylates in moderate to good yields. The *N*-sulfonyl group present in the ketimine was incorporated into the products as a synthetically valuable sulfonate group, which could be further derivatised through a range of methodologies.

2.9 References and Notes

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Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 3: Three-Stage Synthesis of 2,3- and 2,3,5-Substituted Pyridine 6-Tosylates

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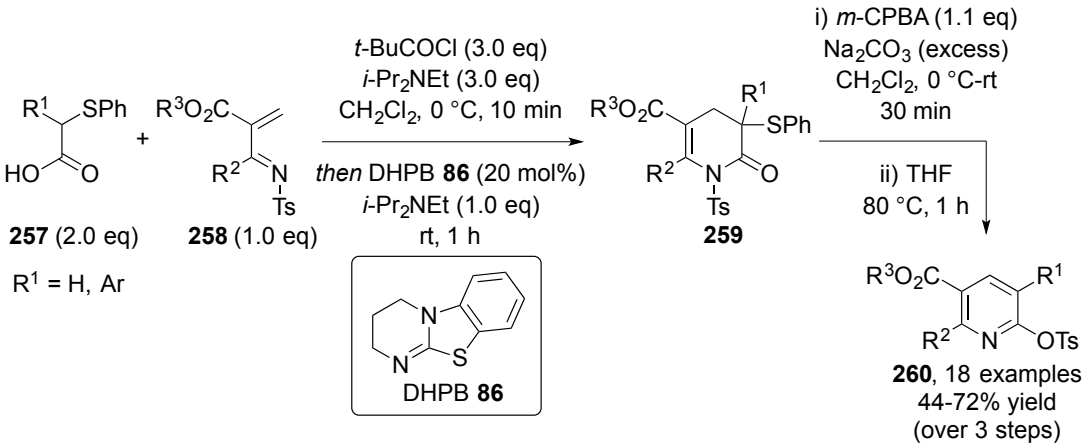
Chapter 3: Three-Stage Synthesis of Tri- and Tetra-Substituted Pyridines

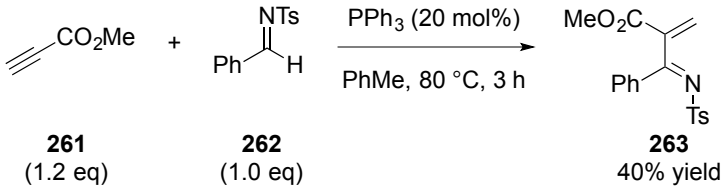
Having demonstrated a catalytic route to 2,4,6-substituted pyridines (Chapter 2) this chapter describes the exploration of further organocatalytic methods towards the synthesis of pyridine derivatives with the successful development of a three-stage isothiourea-mediated protocol. The first step consists of a DHPB **86**-catalysed Michael addition-lactamisation with (phenylthio)acetic acids **257** and 2-*N*-tosyliminoacrylates **258** providing dihydropyridinones **259**. Subsequent *S*-oxidation-sulfoxide elimination process gives an intermediate pyridone that, following an *N*- to *O*-sulfonyl transfer produces the corresponding 2,3- and 2,3,5-substituted pyridine 6-tosylates **260** (Scheme 46).[85]



Scheme 46 - Isothiourea-mediated three-stage synthesis of pyridines.

1.1 Initial Investigation

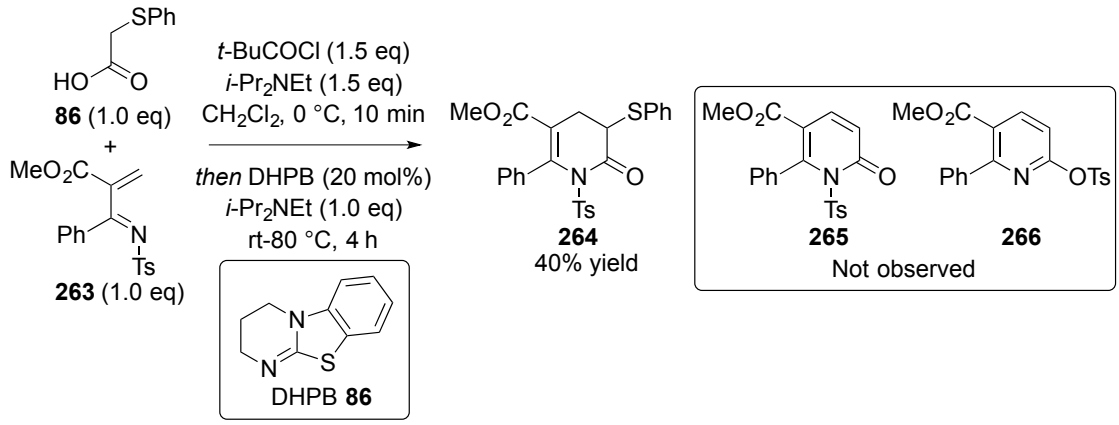
Looking to expand upon the pyridine substituent classes accessible by isothiourea-catalysis through the use of various Michael acceptors, 2-aryl-*N*-tosyliminoacrylate **263** was synthesised in 40% yield using the procedure of Tong and co-workers (Scheme 47).[86]



Scheme 47 - Synthesis of 2-aryl-*N*-tosyliminoacrylates.

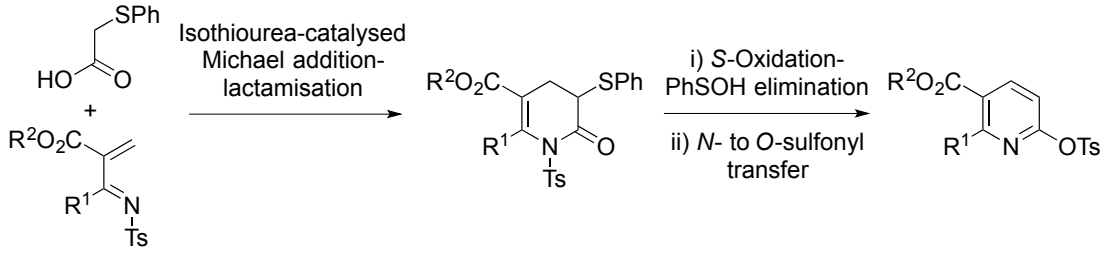
The ketimine Michael acceptor **263** was submitted to the optimum conditions developed in chapter 2 in an attempt to access the corresponding 2,3-pyridine 6-tosylate (Scheme 48). However, treatment of **263** with (phenylthio)acetic acid, *i*-Pr_2NEt and DHPB **86** provided dihydropyridinone **264** in 40% yield, with no observation of either the desired pyridine **266** or the corresponding intermediate pyridone **265**. The use of more forcing basic conditions

applying large excesses of either *i*-Pr_2NEt or Et_3N were also not successful with only **264** returned.



Scheme 48 - Application of 2-aryl-*N*-tosyliminoacrylate 263 to the isothiourea-mediated one-pot cascade conditions.

The lack of **266** formed in this initial reaction suggests that removal of the electron-withdrawing trifluoromethyl or ester substituent from the C(4) position of the dihydropyridinone (as present in examples described in Chapter 2) leads to the proton at that position being significantly less acidic and therefore making a base-mediated elimination of PhSH difficult. However, it was postulated that oxidation of the sulfide to a sulfoxide, followed by elimination may provide access to the intended pyridone intermediate that could then be converted into the desired pyridine *via N*- to *O*-sulfonyl transfer (Scheme 49).



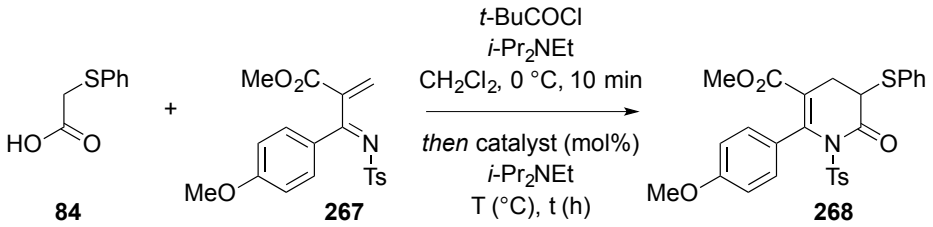
Scheme 49 - Three-stage strategy towards the synthesis of functionalised pyridines.

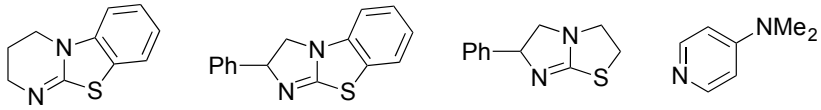
3.1 Process Optimisation

3.1.1 Michael Addition-Lactamisation

Development of this three-stage synthesis of pyridines was initiated with an optimisation of the Michael addition-lactamisation process (Table 11). Using CH_2Cl_2 as the reaction solvent and conducting the reaction at rt gave only 30% conversion (as determined by ^{1}H NMR spectroscopy) after 16 h. To improve the conversion, two equivalents of **84** were used leading to full consumption of **267** within 1 h and after purification an improved isolated yield of 70%. Alternative Lewis base catalysts were screened but with no improvement to that

observed with DHPB **86**. Catalyst loadings of **86** can be reduced to either 10% or 5%, but result in lower yields of 55% and 43%, respectively.





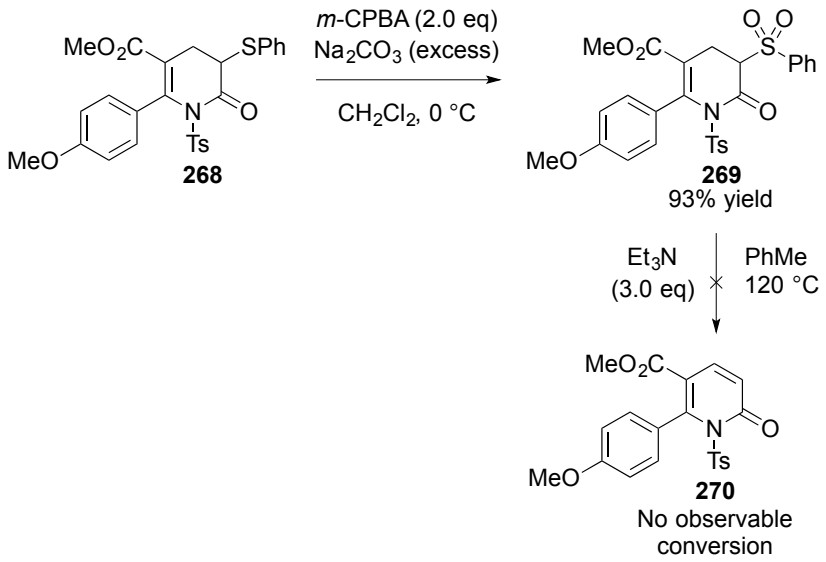
Entry	84 Equivalents[a]	Catalyst (mol%)	Solvent[b]	T (°C)	t (h)	Yield (%)[c]
1	1.0	DHPB (20)	CH_2Cl_2	rt	16	–[d]
2	2.0	DHPB (20)	CH_2Cl_2	rt	1	70
3	2.0	BTM (20)	CH_2Cl_2	rt	1	65
4	2.0	TM (20)	CH_2Cl_2	rt	1	62
5	2.0	DMAP (20)	CH_2Cl_2	rt	1	58
6	2.0	DHPB (10)	CH_2Cl_2	rt	1	55
7	2.0	DHPB (5)	CH_2Cl_2	rt	1	43

[a]1.5 eq of *t*-BuCOCl and *i*-Pr_2NEt applied with respect to acid **84**. [b][0.06 M in **267**]. [c]Isolated yield following column chromatography. [d]30% conversion by ^{1}H NMR, product not isolated.

Table 11 - Michael addition-lactamisation optimisation.

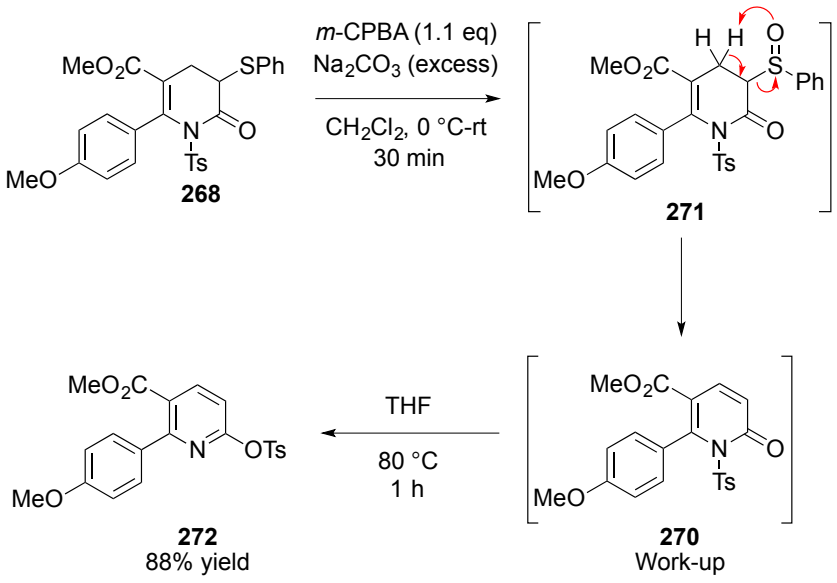
3.1.2 Transformation of Dihydropyridinones into Functionalised Pyridine Tosylates

With the Lewis base-catalysed Michael addition-lactamisation established, attention was next turned to the subsequent elimination step. The first attempt at an *S*-oxidation-sulfoxide elimination was conducted using the procedure from Smith and co-workers, applying *m*-CPBA as the oxidant (Scheme 50).[87] However, this reaction led to over oxidation into sulfone **269**. Elimination of the sulfone substituent was tried using excess Et_3N at an elevated temperature of 120 °C, but with no success.



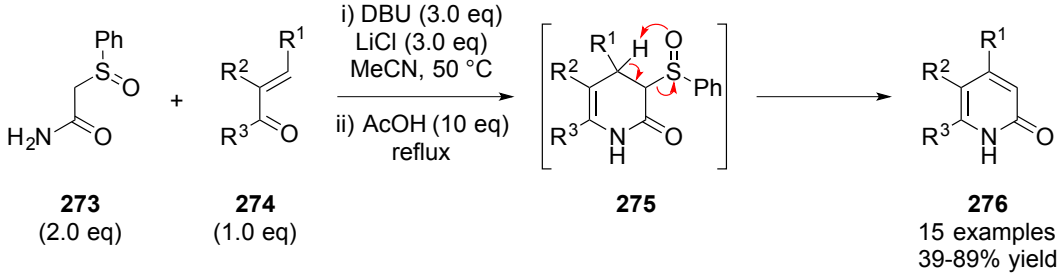
Scheme 50 - Initial attempt at an *S*-oxidation/sulfoxide-elimination protocol.

An optimisation of the oxidation of dihydropyridinone sulfide **268** was conducted with *m*-CPBA selected as the oxidant. The major obstacle was to limit the formation of any over-oxidised sulfone product **269** as purification of the desired pyridone or pyridine became tough due to co-elution of the products. It was finally established that dropwise addition of a [0.3M] solution of *m*-CPBA (1.1 eq) in CH_2Cl_2 to a [0.04 M] solution of **268** and Na_2CO_3 (excess) in CH_2Cl_2 at 0 °C was key for this method (Scheme 51). The reaction can then be warmed to rt and stirred for 30 min. This procedure allows complete conversion of **268** into pyridone **270** without any formation of the undesired sulfone **269**. Simple work-up to remove the 3-chlorobenzoic acid by-product followed by heating in THF at 80 °C for 1 h, to promote the *N*- to *O*-sulfonyl transfer, provided pyridine **272** in 88% yield (62% yield over the three-steps).



Scheme 51 - *S*-oxidation/sulfoxide-elimination protocol.

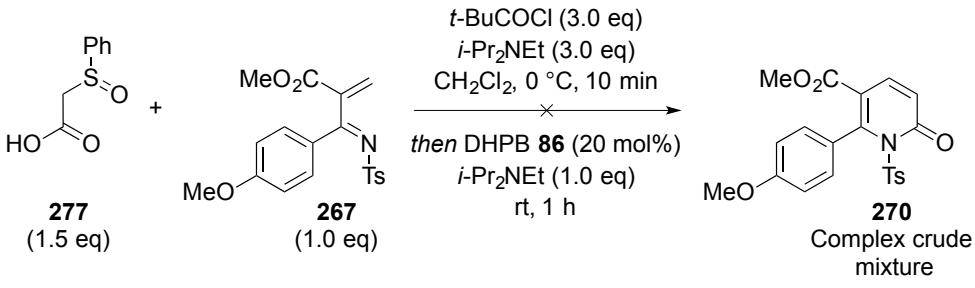
In 2013, Fukuyama and co-workers reported the use of 2-(phenylsulfinyl)acetamide **273** and enones **274** in the DBU-mediated synthesis of pyridones **276** consisting of an *in situ* sulfoxide elimination of dihydropyridinones **275**.[88]



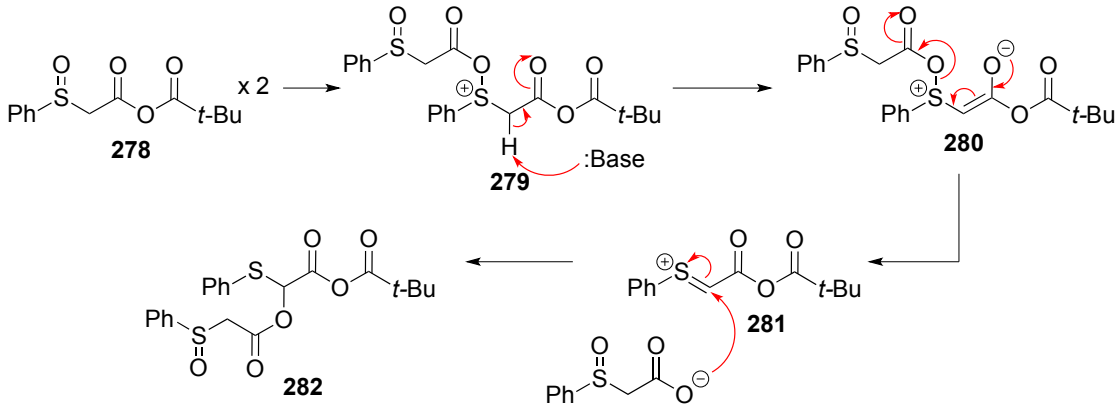
Scheme 52 - Reported synthesis of pyridones using 2-(phenylsulfinyl)acetamide.

Based on this report it was proposed that the use of 2-(phenylsulfinyl)acetic acid **277** may be used directly in the Michael addition-lactamisation system and hence eliminate the additional oxidation step. Unfortunately, reaction of **277** did not furnish pyridone **270** and instead led to a complex crude mixture. One tentative explanation could arise from a competing Pummerer-type rearrangement to give product **282**. Following *in situ* formation of the mixed anhydride **278**, a second molecule of **279** can be susceptible to sulfoxide acylation leading to intermediate **280**. Under the basic reaction conditions, **280** can undergo an elimination to form thionium product **281** that, in the presence of a nucleophile such as the carboxylate anion eliminated in the second step, can be attacked to form Pummerer-type product **283**.

a.) Attempted use of 2-(phenylsulfinyl)acetic acid 277



b.) Proposed Pummerer-type rearrangement

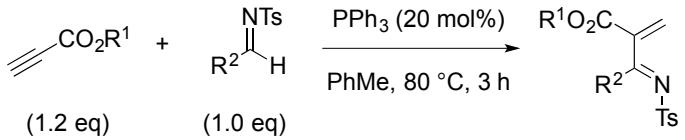


Scheme 53 - a.) Attempted use of 2-(phenylsulfinyl)acetic acid 274. b.) Potential competing Pummerer-type rearrangement.

3.2 Substrate Scope: Synthesis of 2,3-Pyridine 6-Tosylates

3.2.1 Preparation of 2-Aryl-*N*-Tosyliminoacrylates

A range of 2-aryl-*N*-tosyliminoacrylates was synthesised to assess the scope and generality of this process using the protocol from Tong and co-workers (Table 12).[86] Slow-addition of a solution of propiolate in toluene to a solution of the required aldimine in toluene at 80 °C, in the presence of catalytic PPh_3, gives the desired ketimine Michael acceptors **283**-**295** in typically moderate yields. In all cases, particular care must be taken with slow adding of a solution of the propiolate over 3 h to minimise any dimerisation or polymerisation. The procedure works well for electron-neutral and electron-rich aryl aldimines, whereas aryl groups containing electron-withdrawing groups, ortho-substitution or alkyl aldimines proved recalcitrant and returned only starting materials.



(1.2 eq) (1.0 eq)

Entry	Compound No.	R^1	R^2	Yield (%)[a]
1	**283**	Me	Ph	40
2	**284**	Me	3-MeC_6H_4	52
3	**285**	Me	3,5-xylyl	64
4	**286**	Me	4-MeC_6H_4	60
5	**287**	Me	4-BrC_6H_4	42
6	**288**	Me	4-ClC_6H_4	38
7	**289**	Me	2-ClC_6H_4	–[b]
8	**290**	Me	2-Np	42
9	**291**	Me	2-thienyl	32[c]
10	**292**	Me	2-$MeOC_6H_4$	–[b]
11	**293**	Me	4-$CF_3C_6H_4$	–[b]
12	**294**	Me	4-FC_6H_4	–[b]
13	**295**	Me	*t*-Bu	–[b]
14	**296**	Bn	Ph	15

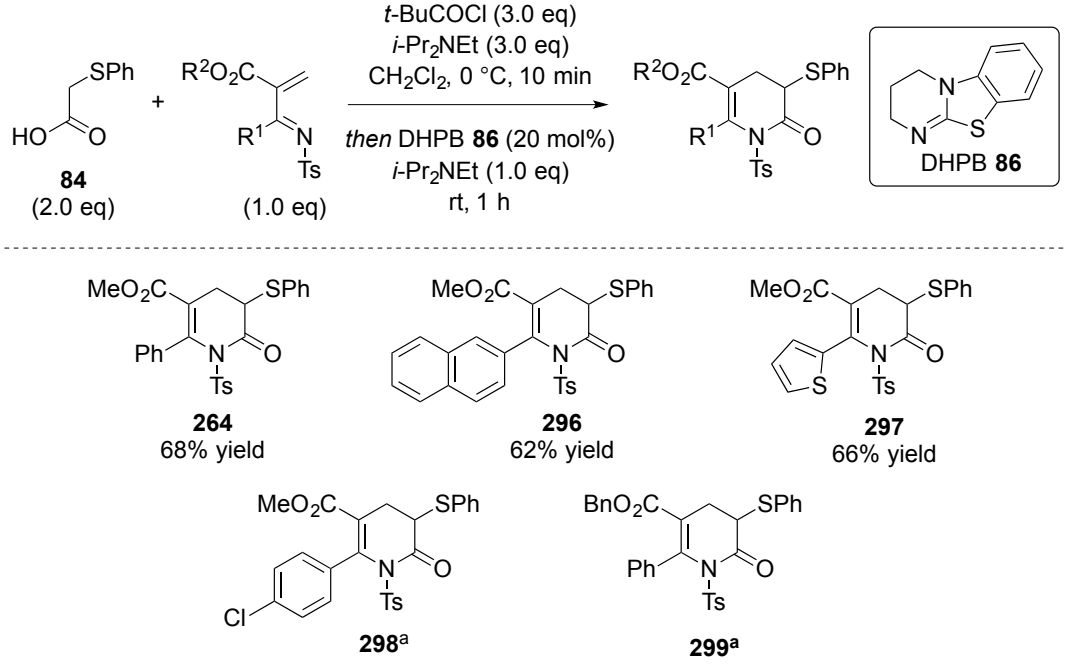
[a]Isolated following column chromatography. [b]Did not provide product. [c]Isolated following preparative HPLC

Table 12 – Synthesis of 2-aryl-*N*-tosyliminoacrylates.

3.2.2 Michael Addition-Lactamisations Applying (Phenylthio)acetic acid 84

The next stage was to examine a selection of the prepared Michael acceptors in the optimised Michael addition-lactamisation conditions with (phenylthio)acetic acid **84** and isothiourea catalyst DHPB **86** (Table 13). The electron-neutral groups of Ph and 2-Np can be installed into the products to give **264** in 68% yield and **296** in 62% yield. Heteroaryl thiophene

is well tolerated and provides product **297** in 66% yield. The halogenated 4-ClC_6H_4 example **298** and Bn ester example **299** were both produced with full consumption of their respective imines observed by ^{1}H NMR spectroscopy. However the isolation of products proved difficult, leading to both **298** and **299** being obtained in 80-90% purity (as determined by ^{1}H NMR spectroscopy). The contaminant could not be clearly characterised and appeared to be decomposition material. These dihydropyridinones were therefore carried forward in the sequence as their crude mixtures.

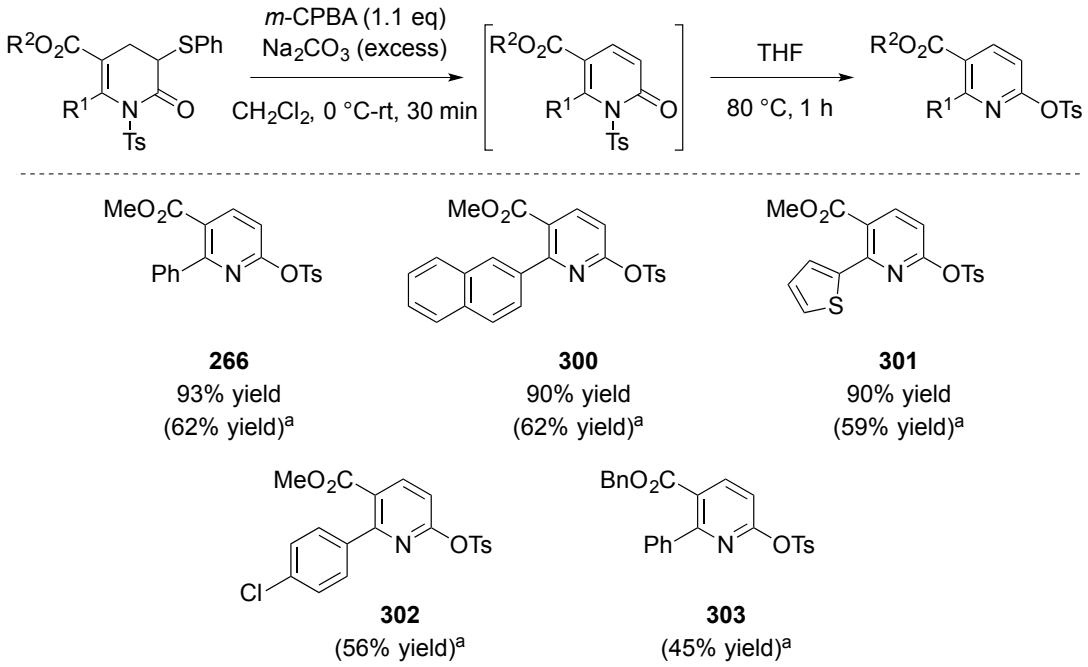


[a]Carried forward as crude mixture of 80-90% purity.

Table 13 - Subsrate scope: Isothiourea-catalysed synthesis of tri-substituted dihydropyridinones.

3.2.3 *S*-Oxidation-Sulfoxide Elimination/*N*- to *O*-Sulfonyl Transfer

Subjecting dihydropyridinones **264**-**296** to the subsequent *S*-oxidation/sulfoxide-elimination/*N*- to *O*-sulfonyl transfer steps proved very successful with excellent conversions observed into the desired tri-substituted pyridines (Table 14). Pyridine **267** displaying the Ph 6-substituent was obtained in excellent 62% yield over the three-steps while, polyaromatic product **300** was produced in 54% yield overall and thienyl pyridine **301** was isolated in 59% yield. As dihydropyranones **295** and **296** were carried forward as crude residues the corresponding yields of the final pyridines were expectantly lower. Pyridine **302** containing the 4-ClC_6H_4 group was produced in 56% yield and the Bn ester pyridine **303** was accessed in a moderate 45% overall yield.



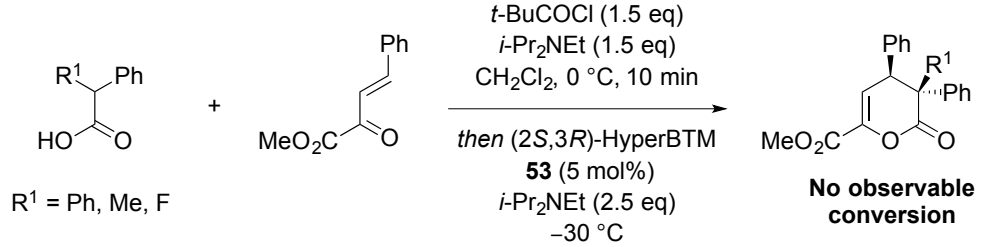
[a]Yield over three-steps.

Table 14 - Substrate scope: synthesis of 2,3-substituted pyridine 6-tosylates.

3.3 Substrate Scope: Synthesis of 2,3,5-Pyridine 6-Tosylates

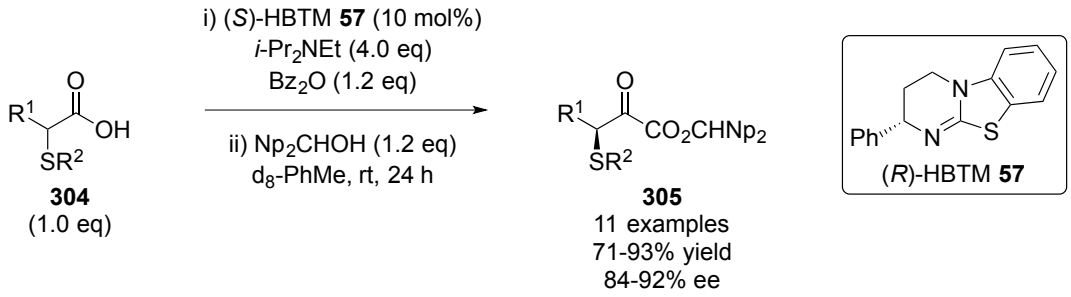
3.3.1 Initial Results

To the point of conducting this project, the use of α,α-disubstituted carboxylic acids in isothiourea ammonium enolate catalysis has proven challenging. In all attempted cases within the Smith group to date the application of such enolate precursors led to no conversion into the desired products. This is assumed to be a result of higher steric demand influencing the deprotonation to the ammonium enolate or a lack of reactivity of the more bulky resultant enolate.



Scheme 54 - Previous attempts to use α,α-disubstituted carboxylic acids.

In 2011, Birman reported a dynamic kinetic resolution of α-(arylthio)- and α-(alkylthio)alkanoic acids **304** using isothiourea catalyst (*S*)-HBTM (10 mol%) in an acylative process to give esters **305**. This report indicated that α-substituted α-sulfide-carboxylic acids are able to form ammonium enolate intermediates.



Scheme 55 - DKR of α-(arylthio)- and α-(alkylthio)alkanoic acids using isothioureas.

Based on the report from Birman, it was envisioned that these enolate precursors in combination with β-unsubstituted Michael acceptors might improve the prospect of reactivity, compared to the previous attempts. In this case it is assumed that the β-unsubstituted Michael acceptor allows for the extra steric demand imposed by the α,α-disubstituted enolate during the initial Michael addition step. Using the Heathcock model previously suggested for these systems the favoured pre-transition state assembly **306** shows higher steric congestion when using β-substituted Michael acceptors and an α,α-disubstituted enolate. Inputting 2-aryl-*N*-tosyliminoacrylates into this model shows fewer significant interactions in favoured pre-transition state assembly **307**. Furthermore, an additional and perhaps key contributing factor is the presence of the sulfide. In previous systems, the groups present at the α-position have been either alkyl or aryl. In this case it can be suggested that the sulfide linkage may orientate the Ph substituent away in a more distal location from the Michael addition reaction centre.

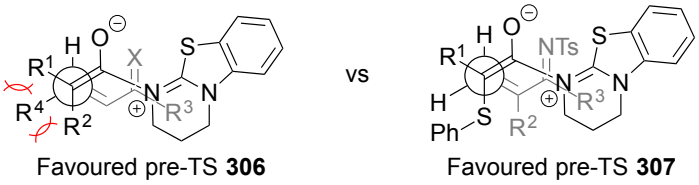
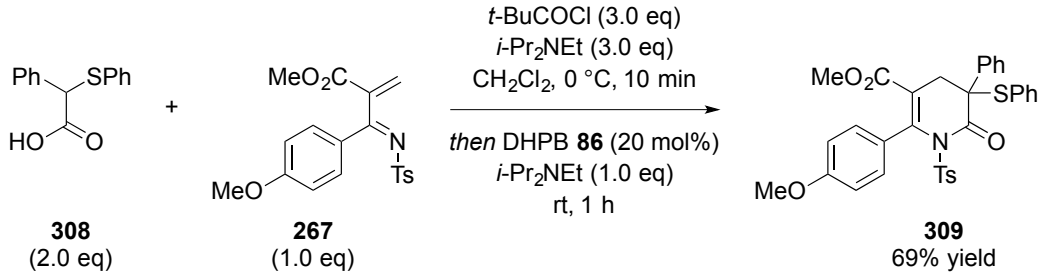


Figure 27 - Proposed rationale for combining β-unsubstituted Michael acceptors and α-substituted α-sulfide carboxylic acids.

Pleasingly, in this case, with the application of 2-aryl-*N*-tosyliminoacrylates, this previous limitation was not apparent (Scheme 56). Dihydropyridinone was produced in 69% yield, under the optimum conditions used already in this protocol, from ketimine **267** and commercially available (phenylthio)phenyl acetic acid **308**.

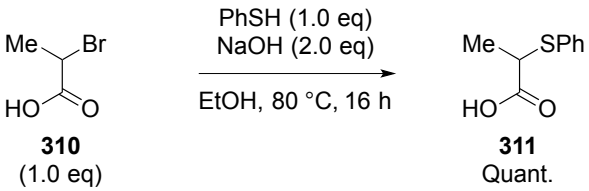


Scheme 56 - Successful application of (phenylthio)phenyl acetic acid 308 with ketimine 267 in isothiourea-catalysed Michael addition-lactamisation.

3.3.2 Preparation of α-Substituted α-Phenylthio Carboxylic Acids

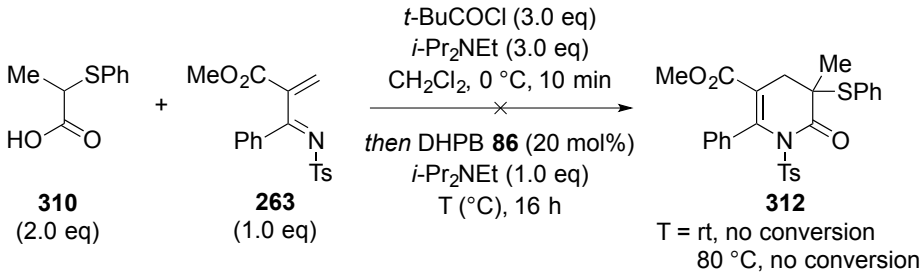
With this successful result in hand it was intended to look further into the scope of disubstituted acids in this system. 2-(Phenylthio)propanoic acid **311** could be synthesised using the procedure from Gualtieri and co-workers (Scheme 57a). Starting from bromopropanionic acid **310**, substitution with PhSH under basic conditions in EtOH provided **311** in quantitative yield. Treatment of **311** under the optimum reaction conditions provided no observation of the desired dihydropyridinone at rt or elevated temperature of 80 °C (Scheme 57b).

a.) Synthesis of 2-(phenylthio)propanoic acid 311



310 (1.0 eq) **311** Quant.

b.) Reactivity of 2-(phenylthio)propanoic acid 311

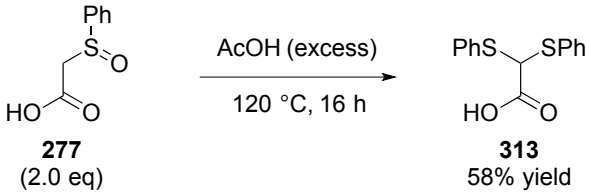


310 (2.0 eq) **263** (1.0 eq) **312** T = rt, no conversion; 80 °C, no conversion

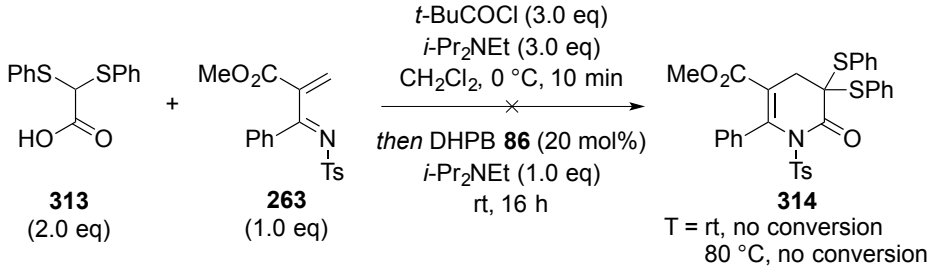
Scheme 57 - Synthesis and reactivity of 2-(Phenylthio)propanoic acid 311.

As the sulfide substituents present on the carboxylic acid may be key for allowing this reaction to be successful, the use of (diphenylthio)acetic acid **313** was investigated. Synthesis of this originates from the procedure of Kenney and co-workers (Scheme 58a),[89] with treatment of (phenylsulfinyl)acetic acid **277** with glacial acetic acid at 120 °C giving **313** in 58% yield. Unfortunately, application of **313** in the Michael addition-lactamisation gave no conversion to dihydropyridinone **314** (Scheme 58b).

a.) Synthesis of (diphenylthio)acetic acid 313



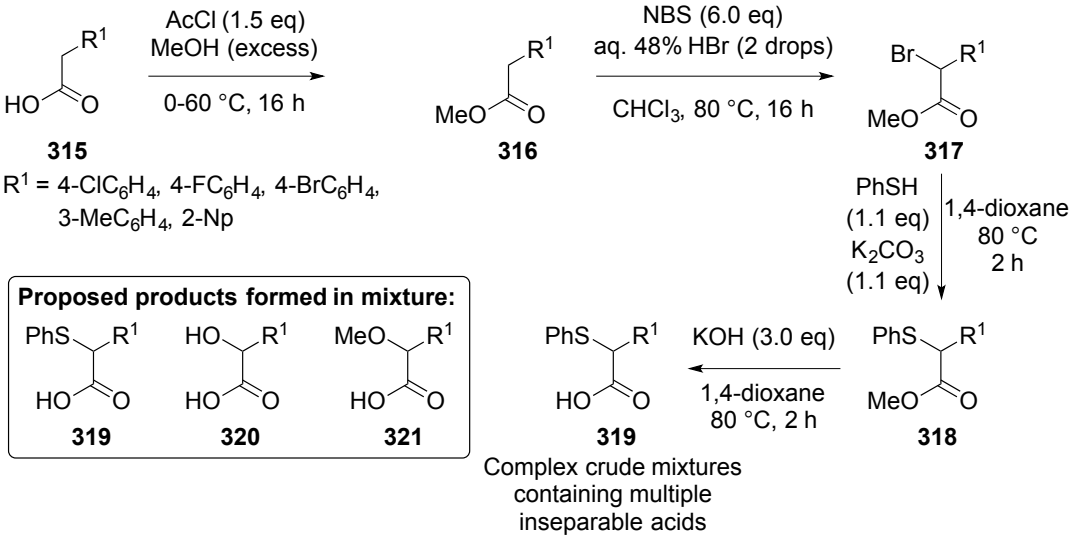
b.) Reactivity of (diphenylthio)acetic acid 314



Scheme 58 - Synthesis and reactivity of (diphenylthio)acetic acid 313.

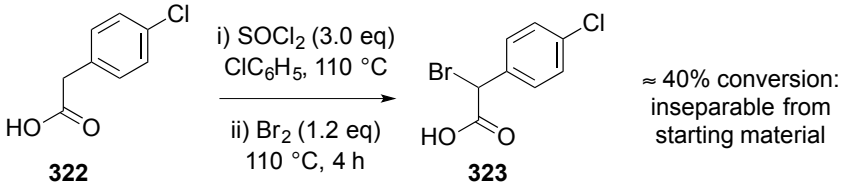
These two results imply that the presence of an aryl group at the α-position is key for reactivity. An explanation may be that the α-proton in the α-aryl-α-phenylthioacetic acids has a pKa suitable for deprotonation to the ammonium enolate with the resulting enolate possessing the required nucleophilicity and reactivity.

Preparation of a range of further α-aryl-α-phenylthioacetic acids was, however, difficult. The first strategy was to conduct bromination and subsequent substitution with PhSH on the corresponding methyl esters (Scheme 59). It was envisioned that the purification of the ester products would be significantly easier using column chromatography compared with the carboxylic acids. The first step was to convert the commercially available carboxylic acids **315** into their methyl esters **316**, with quantitative yields obtained in all cases. Bromination using NBS and substoichiometric aq. 48% HBr, provided the bromo esters in typically good yield. Following this, the bromide was substituted with PhSH under basic conditions. The majority of problems encountered with this synthetic strategy were encountered in the final hydrolysis step. In all cases a complex mixture of carboxylic acid products were obtained that could not be separated by column chromatography (using TFA eluent additive). Analysis of the crude reaction by ^{1}H NMR spectroscopy suggested that the product distribution might consist of the desired product **319**, mandelic acid derivative **320** and methoxy-acid **321**. The latter two products arising from potential substitution of the sulfide with H_2O or the methoxide anion eliminated from the ester hydrolysis step.



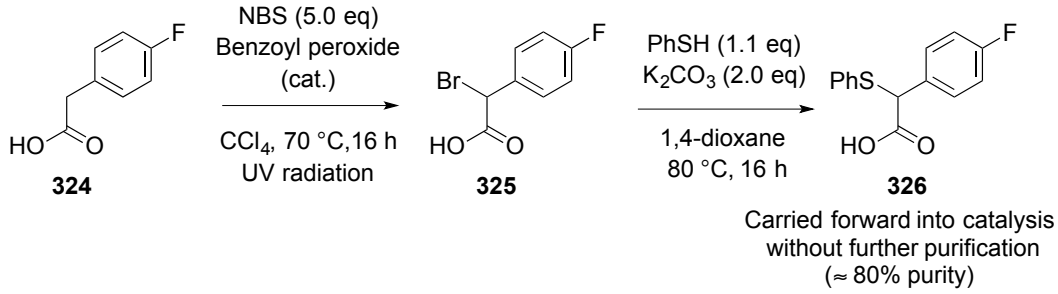
Scheme 59 - Initial synthetic attempts towards α-substituted (phenylthio)acetic acids.

The next attempt looked to access bromo-acid **313** directly from **322** by forming the acid chloride *in situ* and then slow addition of bromine. The reaction was heated in chlorobenzene at 110 °C with the best conversion observed being 40% (as determined by ^{1}H NMR spectroscopy). The nature of both starting material **322** and product **323** being carboxylic acids made separation difficult. As the Michael addition-lactamisation protocol applies carboxylic acids as the enolate precursors, a mixture of acids was not suitable to be carried forward.



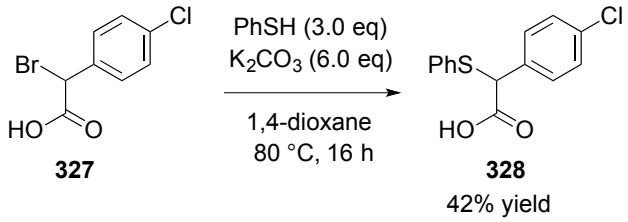
Scheme 60 - Attempted synthesis of 323 *via* an acid chloride α-bromination reaction.

There is some precedent in the chemical literature for successfully conducting related α-brominations on acids and esters using radical bromination approaches. A procedure was therefore devised that applied benzoyl peroxide as the radical initiator and NBS as the brominating agent under the exposure of UV-radiation (Scheme 61). After some optimisation it was found that freshly recrystallised NBS and freshly distilled CCl_4 were necessary for full conversion. Although product **326** could not be fully purified (obtained as 90% pure by ^{1}H NMR spectroscopy) the key feature was the full consumption of **325** was observed. The bromo-acid **325** could then be subject to the PhSH substitution reaction giving **326**. Once more this was obtained as a crude mixture consisting of only one carboxylic acid product. It was deemed that this, despite being only ≈ 80% pure by ^{1}H NMR analysis, could be carried forward into the isothiourea-catalysis.



Scheme 61 - Devised synthetic route to carboxylic acid 326.

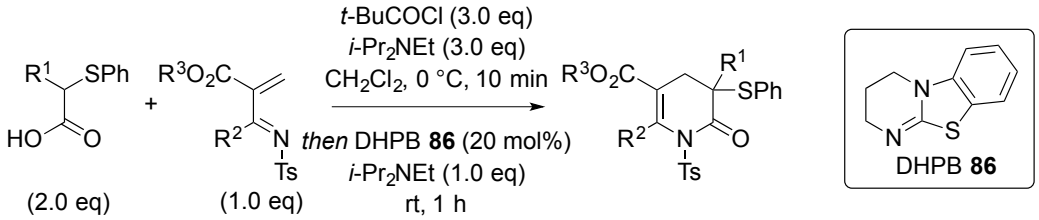
At this time, bromo-acid **327** became commercially available and therefore allowed the synthesis of 2-(4-chlorophenyl)-2-(phenylthio)acetic acid **328** through the PhSH substitution reaction (Scheme 62). In this case, the equivalence of PhSH and K_2CO_3 were increased to give full conversion, with **328** isolated in 42% yield.

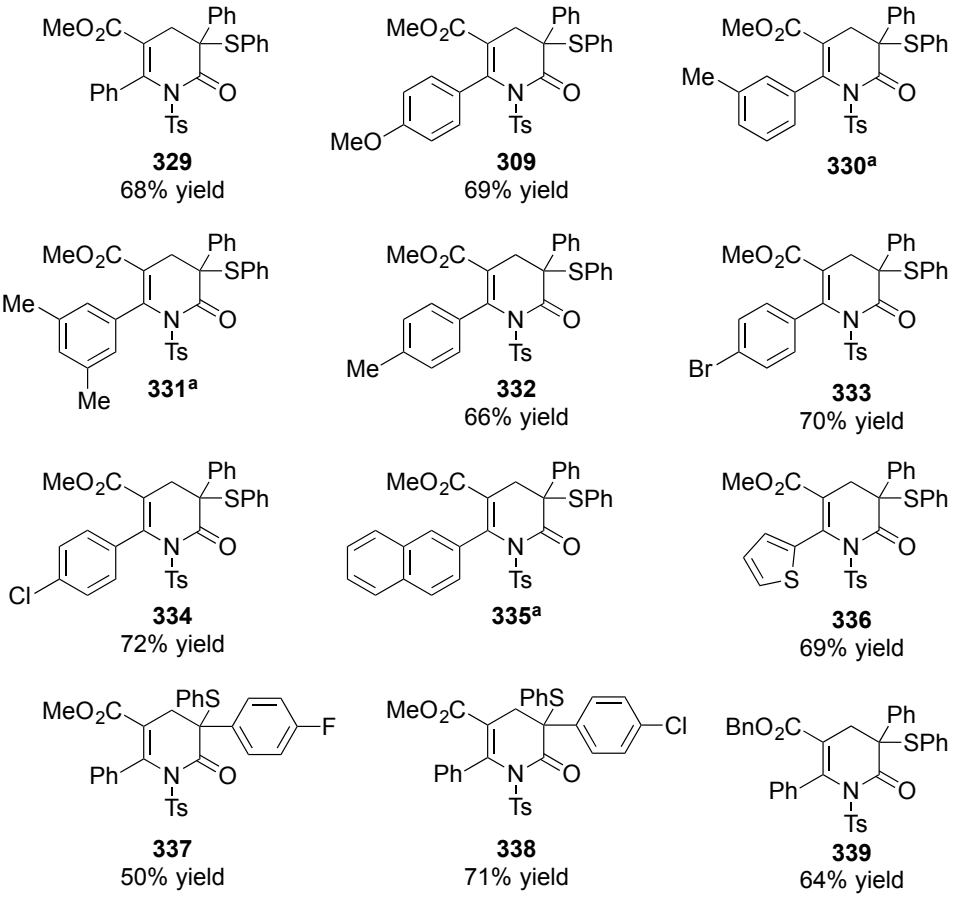


Scheme 62 - Synthesis of carboxylic acid 328.

3.3.3 Michael Addition-Lactamisation Applying α,α-Disubstituted (Phenylthio)acetic Acids

The isothiourea-catalysed Michael addition-lactamisation process tolerates a wide range of 2-aryl-*N*-tosyliminoacrylates when applying (phenylthio)phenyl acetic acid **308** as the enolate precursor (Table 15). Diphenyl dihydropyridinone **329** was formed in excellent 77% yield. 3-Tolyl, 3,5-xylyl and 2-Np examples, **330**, **331** and **335,** proceeded with full consumption of Michael acceptor, however, the products could only be purified ≈80-90% purity (determined by ^{1}H NMR spectroscopy). 4-Tolyl containing dihydropyridinone **332** was synthesised in good 60% isolated yield. Halogenated products **333** and **334** could be accessed in good 70% and 72% yield, respectively. Heteroaromatic substituents such as 2-thienyl group was well tolerated giving product **336** in 61% yield. Following the synthesis of α,α-disubstituted acids **326** and **328**, these were applied to the reaction conditions giving dihydropyridinones **337** and **338** in 50% and 64% yields, respectively. The lower yield for **337** can be attributed to the use of carboxylic acid **326** as crude ≈ 80% purity. Alternative ester substituents can be accommodated as shown by example **339**, produced in good 64% yield.





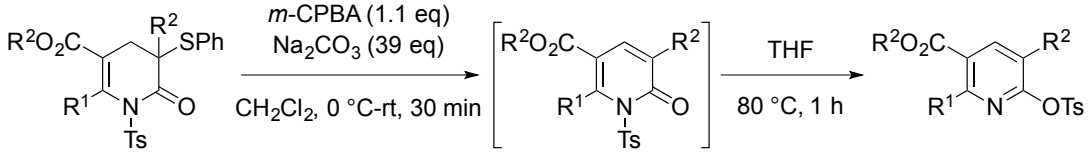
[a]Carried forward as crude mixture of 80-90% purity.

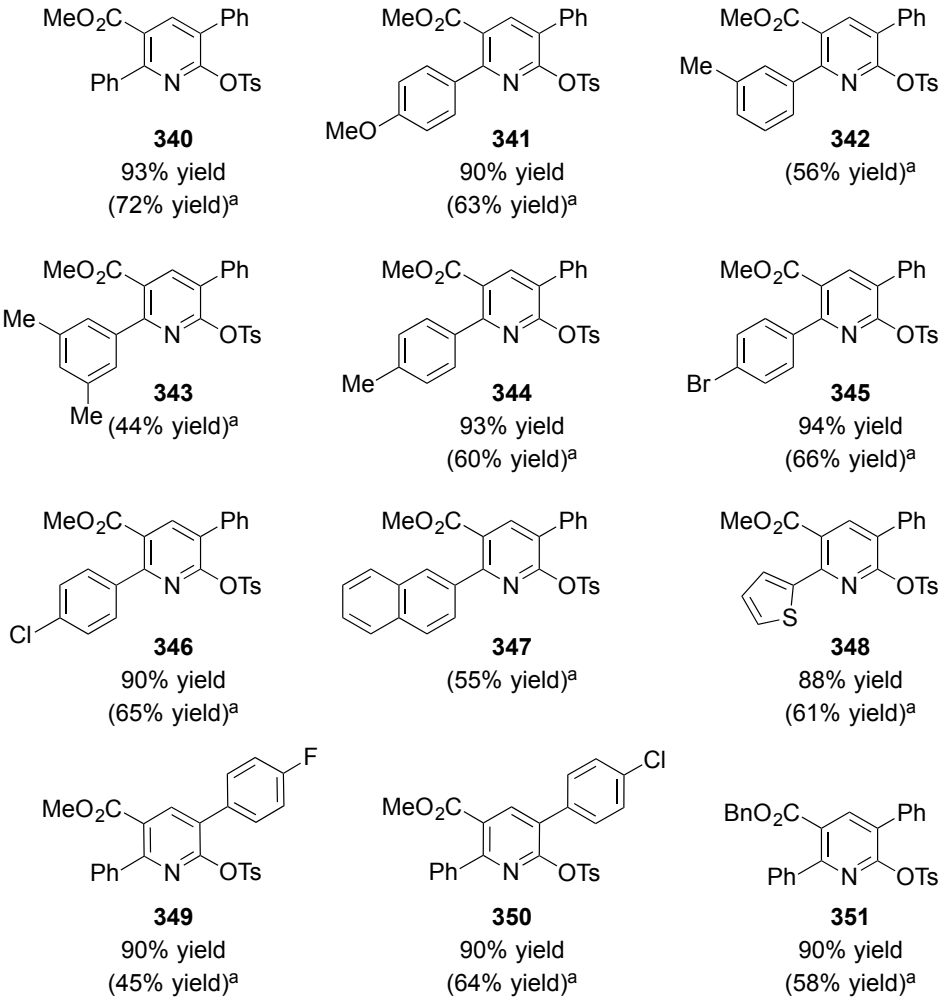
Table 15 - Substrate scope: isothiourea-catalysed synthesis of tetra-substituted dihydropyridinones.

3.3.4 *S*-Oxidation-Sulfoxide Elimination/*N*- to *O*-Sulfonyl Transfer

The tetra-substituted dihydropyridinones were next subject to the *S*-oxidation-sulfoxide elimination/*N*- to *O*-sulfonyl transfer steps (Table 16). Highly substituted pyridines were produced showing excellent levels of conversion in all cases with no remaining starting materials or formation of any major side-products. Diphenyl pyridine **340** was achieved in excellent 72% yield over the three-stage protocol. With dihydropyridinones **330**, **331** and **335** being taken on for the synthesis of pyridines **342**, **343** and **347** as crude mixtures, the resulting overall yields were only moderate (56%, 44% and 55%, respectively). Thienyl pyridine **348** was accessed in a good 61% overall isolated yield. Pleasingly, variation of the 5-substituent was accommodated into the pyridine products **349** and **350** giving yields of 64% and 45%,

respectively. Finally the 3-substituted Bn ester pyridine **351** was provided in moderate 58% yield.





[a]Yield over three-steps.

Table 16 - Substrate scope: synthesis of 2,3,5-substituted pyridine 6-tosylates.

3.4 Scale-Up and Derivatisation

As with the tri-substituted pyridine synthesis described in chapter 2, a key feature is the incorporation of the tosylate functional handle into the pyridine products. It was imagined that transformation of this functional group on both the tri- and tetra-substituted pyridines would provide access to more diverse products and substituent patterns. To accomplish this, the three-stage pyridine protocol was scaled-up to provide large quantities of material as well as showcase the scalability of the process. Starting from 2.0 g (5.36 mmol) of methyl 2-((4-

methoxyphenyl)(tosylimino)methyl)acrylate **367**, pyridines **272** and **341** could be synthesised in 55% and 67%, respectively, over the three-steps of the methodology (Figure 28).

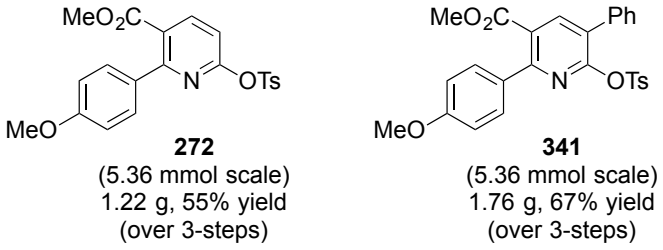
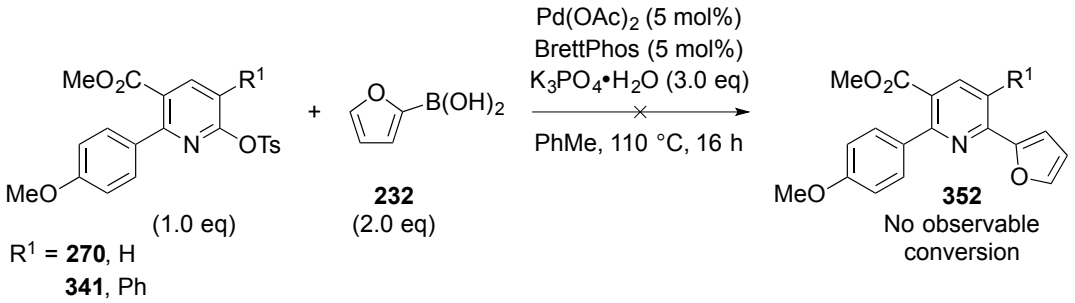


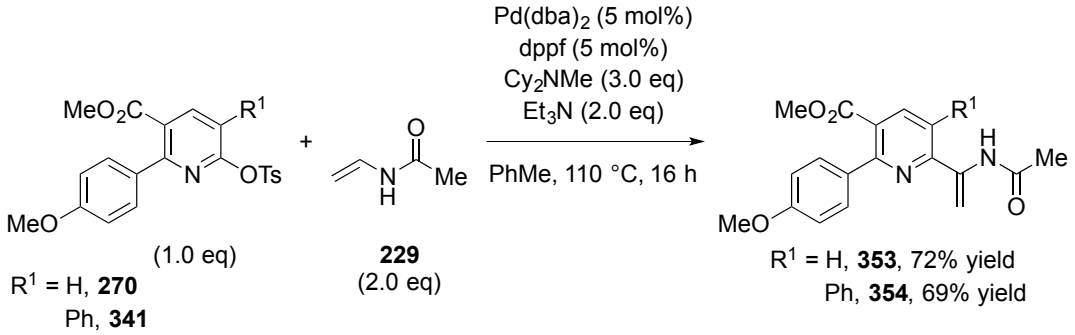
Figure 28 - Scaled-up process for synthesis of 270 and 341.

The first derivatisation attempted was a Suzuki-Miyaura coupling as reported by Buchwald and co-workers (Scheme 63).[79] however treatment of the requisite pyridine with $Pd(OAc)_2$, BrettPhos and $K_3PO_4 \bullet H_2O$ in the presence of furanyl boronic acid **232** gave no sign of the intended furanyl pyridine **352**. These reactions were conducted in both ambient and inert (Ar) atmospheres and at elevated temperatures but with no success.



Scheme 63 - Attempted Suzuki-Miyaura coupling on pyridine 352.

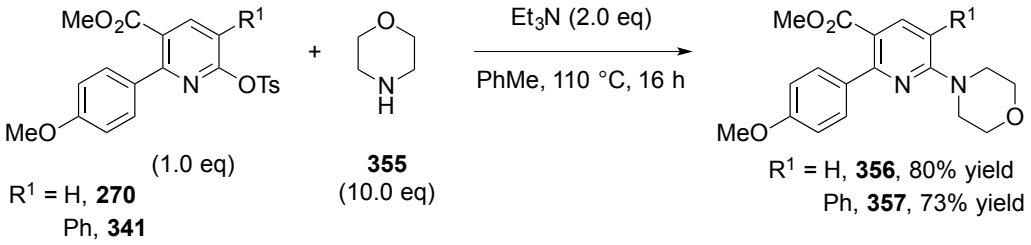
Pleasingly, the Pd-catalysed Mizoroki-Heck coupling described by Skrydstrup and co-workers was successful (Scheme 64).[78] Reaction with either pyridine **270** or **341**, $Pd(dba)_2$, dppf, *N*-vinylacetamide **229** and Cy_2NMe gave products **353** and **354** in 72% and 69% yield, respectively.



Scheme 64 - Mizoroki-Heck reaction on pyridines 270 and 341.

Nucleophilic aromatic substitution with morpholine also works well on both pyridine **271** and **341**, with products **356** and **357** obtained in 80% and 73% yield, respectively (Scheme

65). Both this S_NAr and the Mizoroki-Heck reaction provide access to functionalised 2,3,6- and 2,3,5,6-substituted pyridines.



Scheme 65 - S_NAr reaction on pyridines 270 and 341.

Finally, the tosylate group can be removed through a Pd-catalysed protodetosylation using HCO_3H, $Pd(OAc)_2$, dppp and Et_3N in DMF at 100 °C (Scheme 66).[80] Conducting this transformation broadens this work into the synthesis of 2,3- and 2,3,5-substituted pyridines with the synthesis of **358** in 74% yield and **359** achieved in 78% yield.

Scheme 66 - Protodetosylation reaction on pyridines 270 and 341.

3.5 Conclusion

In conclusion, thiophenyl carboxylic acids and 2-aryl-*N*-tosyliminoacrylates can be efficiently converted into functionalised tri- and tetra-subsituted pyridines. DHPB **86**-mediated Michael addition-lactamisation initiates the synthesis to give a wide range of dihydropyridinones in typically good yield. These products are readily converted into the desired pyridine 6-tosylates through an *m*-CPBA mediated *S*-oxidation-sulfoxide elimination process, followed by a thermal assisted *N*- to *O*-sulfonyl transfer. These highly functionalised products can then be readily derivatised through the tosylate functional group to further elaborate the structure. Overall this procedure provides an efficient organocatalyst-mediated route towards the synthesis of 2,3-, 2,3,6-, 2,3,5- and 2,3,5,6-substituted pyridines.

3.6 References and Notes

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Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 4: Application of 2-Aroyl and 2-Imino Acrylates in Enantioselective Isothiourea-Catalysis

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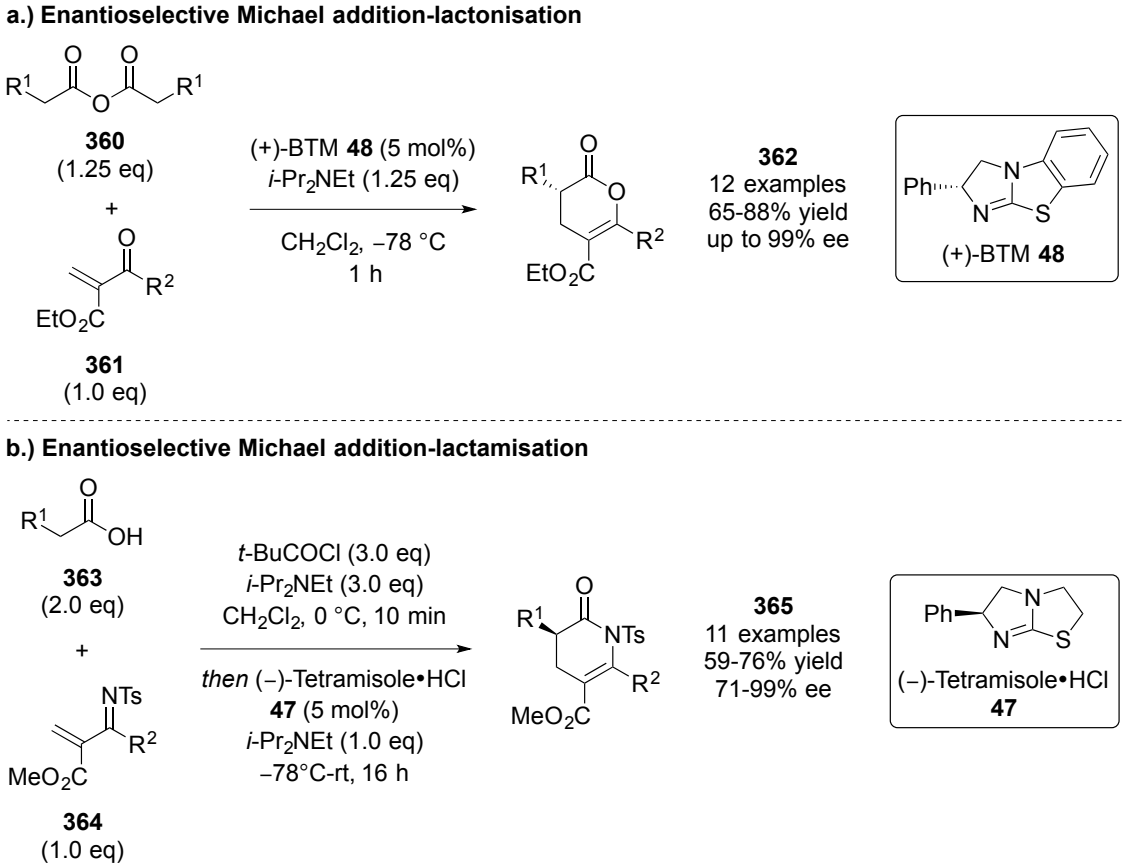
Chapter 4: Application of 2-Aroyl and 2-Imino Acrylates in Enantioselective Isothiourea-Catalysis

This chapter describes the application of aroyl and imino acrylate-type Michael acceptors for the first time in enantioselective isothiourea-catalysis giving the corresponding 3,5,6-subsituted dihydropyranones and 2,3,5-substituted dihydropyridinones. Dihydropyranones **362** are achieved in high enantiocontrol from homoanhydrides **360** and 2-aroylacrylates **361** catalysed by (+)-BTM **48** (5 mol%) (Scheme 67a). Dihydropyridinones **365** are accessed in excellent enantiocontrol from carboxylic acids **363** and 2-*N*-tosyliminoacrylates **364** catalysed by (−)-tetramisole•HCl **47** (5 mol%) (Scheme 67b).

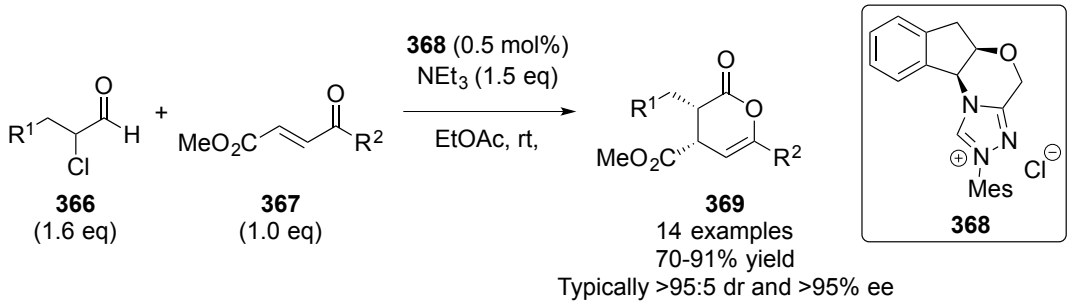


Scheme 67 - a.) Isothiourea-catalysed Michael addition-lactonisation using 2-aroyl acrylates. b.) Isothiourea-catalysed Michael addition-lactamisation using 2-*N*-tosyliminoacrylates.

4.1 Introduction

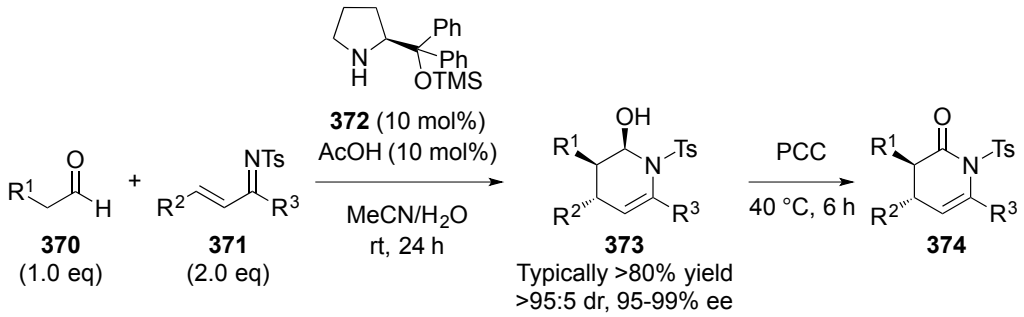
The synthesis of functionalised chiral small molecules through asymmetric catalysis remains a key area within synthetic methodology. Endocyclic enol dihydropyranones and enamine dihydropyridinones are found within bioactive compounds and as a result there has been many efforts towards their production.[90] Classically this can be achieved through uncatalysed-hetero Diels-Alder cycloaddition reactions, with more recent examples involving π-olefin and π-alkyne cyclisations.[91] However, the state-of-the-art methods to form chiral

dihydropyranones and dihydropyridinones with high stereoselectivity remains organocatalytically generated enolate equivalents. N-Heterocyclic carbenes (NHCs) have been used in such a manner to form nucleophilic azolium enolate intermediates.[92] Bode and co-workers described a pioneering example of this in 2006 (Scheme 68).[93] Treatment of α-chloroaldehyde **366** with NHC catalyst **368** (0.5 mol%) in the presence of NEt_3 generates an azolium enolate that can undergo a [4+2] cycloaddition with keto ester **367** to give dihydropyranones **369** in excellent yield and stereoselectivity.



Scheme 68 - NHC-catalysed Diels-Alder reaction by Bode and co-workers.

In 2008, Chen and co-workers reported an enamine-catalysed approach to the synthesis of chiral cyclic hemiaminals **373** that could then be subsequently oxidised into dihydropyridinones **374** (Scheme 69).[94] Reaction of aldehyde **370** and α,β-unsaturated ketimines **371** in the presence of prolinol-derived catalyst **372** (10 mol%) and acetic acid gives an inverse electron-demand Diels-Alder reaction to produce cyclic hemiaminals **373** in typically >80% yield and 95-99% ee and >95:5 dr. Hemiaminal **373** can then be readily oxidised with PCC to provide dihydropyridinones **374**.



Scheme 69 - Enamine-catalysed asymmetric aza-Diels-Alder reaction from Chen and co-workers.

As described in Chapter 1, the Smith Group have made a number of contributions to this area through the application of asymmetric isothiourea-generated ammonium enolate catalysis (Figure 29). Throughout all of the previous isothiourea work conducted in the Smith group, as well as the examples described in this introduction, the product substituent classes fall within the 3,4,6-substitution pattern. To the best of our knowledge, the chiral 3,5,6-substituted

dihydropyranones and dihydropyridinones have not been previously produced in enantioselective catalysis.

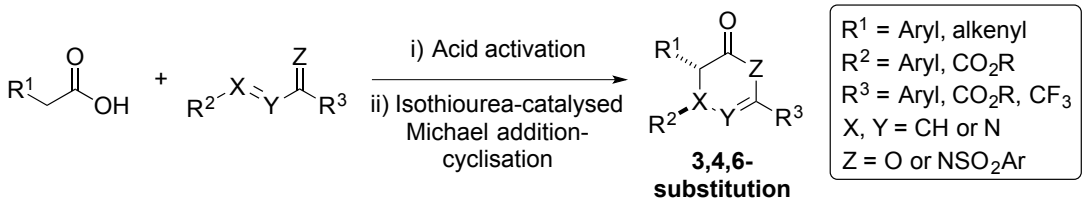


Figure 29 - Overview of Smith Group isothiourea-catalysed Michael addition-cyclisation chemistry.

Following the use of 2-*N*-tosyliminoacrylates in an isothiourea-mediated three-stage synthesis of functionalised pyridines, it was proposed these acrylate-derived Michael acceptors would provide access to chiral 3,5,6-substituted dihydropyranones and 2,3,5-substituted dihydropyridinones in an enantioselective isothiourea-catalysed protocol (Figure 30).

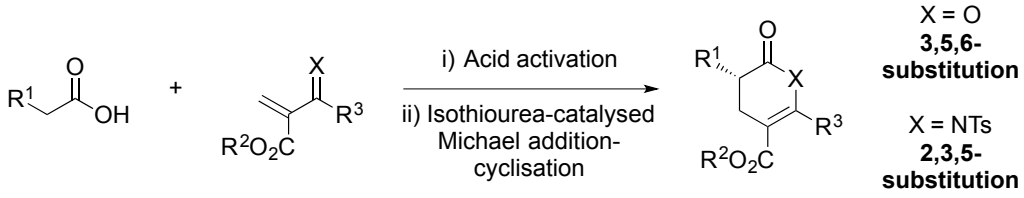
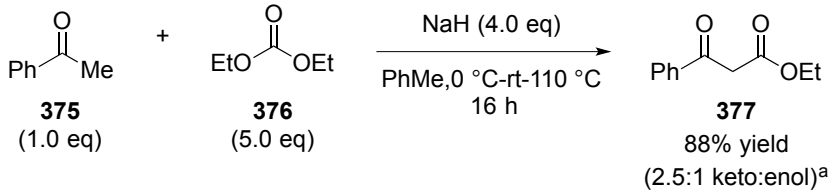


Figure 30 - Enantioselective synthesis of 3,5,6-substituted dihydropyranones and 2,3,5-substituted dihydropyridinones.

4.2 Michael Addition-Lactonisation

4.2.1 Initial Results and Reaction Optimisation

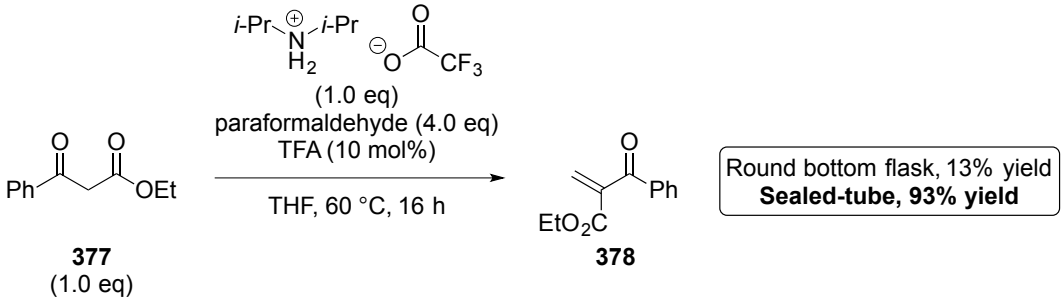
To investigate the isothiourea-catalysed Michael addition-lactonisation protocol to form 3,5,6-substituted dihydropyranones, 2-aroylacrylate Michael acceptors were chosen as potential substrates. This structural class would give the desired substituent pattern, while the ester group should make the Michael acceptor sufficiently electron-deficient to react. The synthetic route to synthesise ethyl 2-benzoylacrylate started with the preparation of β-ketoester **377** using the reported procedure from Bretner and co-workers (Scheme 70).[95] Acetophenone **375** was treated with NaH in PhMe at 0 °C before a solution of diethylester **376** in PhMe was added dropwise. The reaction was warmed to rt over 2h before being heated at 110 °C overnight giving ketoester **377** in 88% yield.



[a]Determined by ^{1}H NMR spectroscopy.

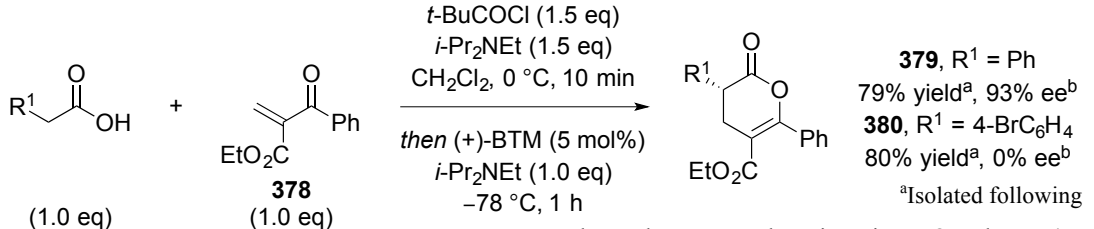
Scheme 70 - Synthesis of β-ketoesters.

Next, ketoester was subject to the methenylation reaction conditions reported by Connell and co-workers (Scheme 71).[96] Ketoester **377**, diisopropylammonium 2,2,2-trifluoroacetate, paraformaldehyde and TFA were stirred at 60 °C overnight to give 2-benzoylacrylate **378** in 13% yield. Following a short optimisation, it was found that conducting this reaction in a sealed-tube significantly improves the conversion to product, **378** in 93% yield.



Scheme 71 – Preparation of 2-benzoylacrylate 378.

Preliminary studies began with the optimisation of the isothiourea-catalysed Michael addition-lactonisation using phenylacetic acid and ethyl 2-benzoylacrylate **378**. Following a screen of catalysts, solvents and temperatures the reaction with pivaloyl chloride, *i*-Pr_2NEt and (+)-BTM (5 mol%) at −78 °C gave dihydropyranone **379** in 79% yield and 93% ee (Scheme 72). Disappointingly, this procedure did not prove general, with the use of an alternative aryl acetic acid giving variable enantioselectivity. For example, when 4-bromophenyl acetic acid was used the corresponding dihydropyranone **380** was produced in good 80% yield but as a racemate.

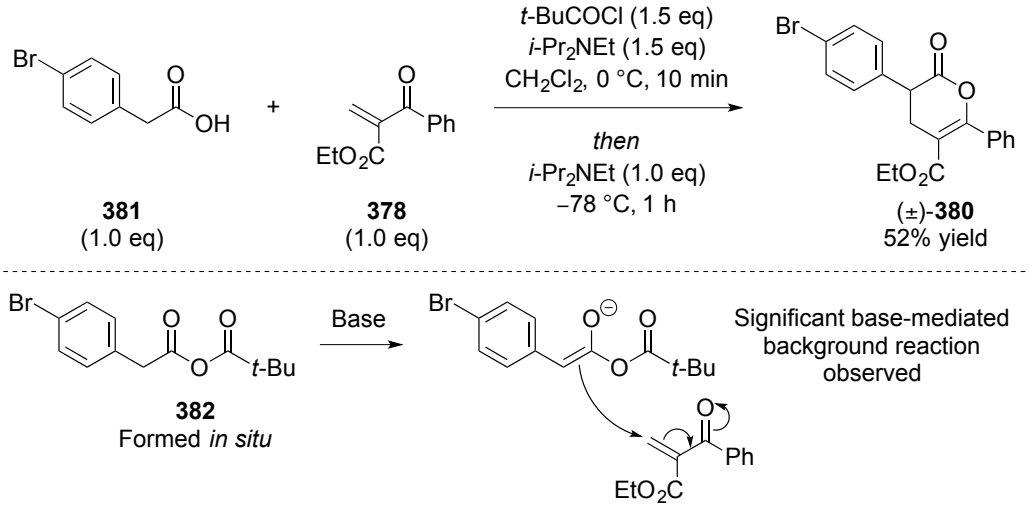


[a]Isolated following column chromatography using Biotage® Isolera™ 4.

[b]Determined by chiral HPLC.

Scheme 72 - Initial attempts at a protocol utilising carboxylic acids.

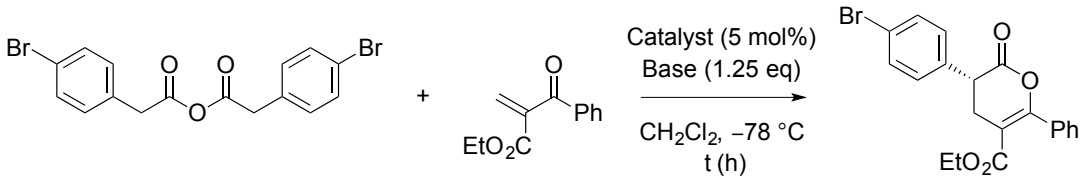
It was proposed that the highly reactive 2-aroyl acrylate **378** may be prone to a competitive base-mediated racemic background reaction. To probe this, a control reaction in absence of (+)-BTM **48** was performed; forming dihydropyranone **380** in 52% yield (Scheme 73). Therefore, this reaction process suffers from significant competition with a racemic background reaction between the *in situ* formed mixed anhydride **382** and **378** that accounts for the low enantioselectivities obtained. The reaction was also tried in the absence of any additional base (*i*-Pr_2NEt) however in these cases only low (<10% conversion by ^1H NMR spectroscopy) was obtained. To overcome the low enantioselectivity observed further optimisation was conducted using 4-bromophenyl acetic acid **381**. However, despite screening a number of bases, temperatures and catalyst the desired product **380** was continually produced with no enantioselectivity. Addition of a solution of **378** (0.25 M in CH_2Cl_2) *via* syringe pump over 2 h gave a slight improvement, with **380** formed in 74% yield and 20% ee.



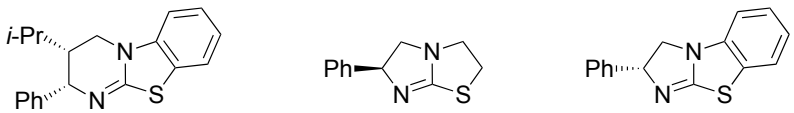
Scheme 73 - Control reaction excluding Lewis base catalyst.

A major breakthrough in this transformation arose from the evaluation of pre-formed homoanhydrides as alternative enolate precursors in place of *in situ* activated carboxylic acids. The Smith group has applied such precursors previously, with one advantage being the reduced levels of organic base necessary for catalysis. Reaction of homoanhydride **383**, 2-aroyl acrylate **378** and (+)-BTM **48** (5 mol%) in the presence of 1.25 eq of *i*-Pr_2NEt gave product **380** in 88% yield and 88% ee. In this system, use of isothiourea catalyst (2*S*,3*R*)-HyperBTM **53** gave **380** in 81% yield but only 46% ee while (−)-tetramisole•HCl **47** gave *ent*-**380** in 80% yield and 78% ee (Table 17). Therefore, (+)-BTM **48** was chosen as the optimum catalyst and carried forward. Lowering the reaction temperature to −78 °C gave **380** after 1 h in 88% yield and excellent 91% ee. The choice of base may have an impact on the competition between the intended isothiourea-catalysed process and the racemic background reaction, therefore various organic and inorganic bases were investigated. Interestingly, the reaction with Et_3N gave a dramatic increase in background reaction, forming **380** in 0% ee. Inorganic bases such as Cs_2CO_3 and

Na_2CO_3 gave product **380** in moderate to good 57% and 83% ee, respectively. Slow syringe pump addition of a solution of *i*-Pr_2NEt (0.25 M in CH_2Cl_2) gave a reduced 70% ee and 88% yield after 2 h.



383 (1.25 eq) **378** (1.0 eq) **380**



(2*S*,3*R*)-HyperBTM **53** (–)-Tetramisole•HCl **47** (+)-BTM **48**

Entry	Lewis base (5 mol%)	T (°C)	t (h)	Base	Yield (%)[a]	ee (%)[b]
1	**48**	rt	0.2	*i*-Pr_2NEt	88	88
2	**53**	rt	0.2	*i*-Pr_2NEt	81	46
3	**47**	rt	0.2	*i*-Pr_2NEt	80	(*ent*) 78[c]
4	**48**	−78 °C	1	*i*-Pr_2NEt	88	91
5	**48**	−78 °C	1	Et_3N	85	0
6	**48**	−78 °C	1	Cs_2CO_3	58	57
7	**48**	−78 °C	1	Na_2CO_3	81	83
8[d]	**48**	−78 °C	2	*i*-Pr_2NEt	88	70

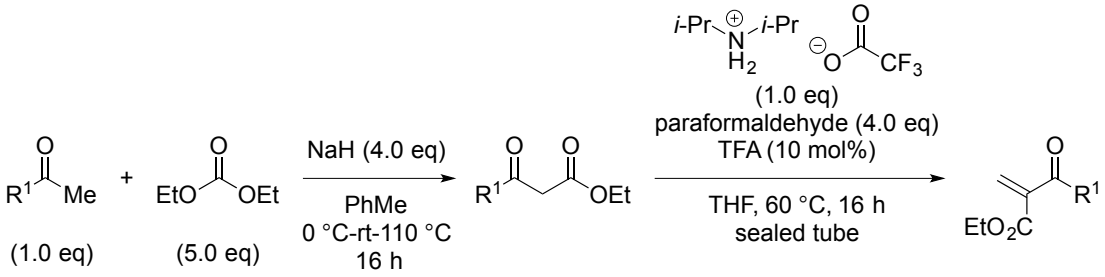
[a]Isolated following column chromatography using Biotage® Isolera™ 4. [b]Determined by chiral HPLC. [c](*S*)-enantiomer obtained. [d]Syringe pump addition of **378** (0.25 M in CH_2Cl_2) over 2 h.

Table 17 - Michael addition-lactonisation reaction optimisation.

Although dihydropyranone **380** can be prepared in high yield and ee through the optimised reactions using homoanhydride **383**, considerable care is needed when performing the reaction to maintain reproducible enantioselectivity. In particular, careful temperature control is essential. Optimisation showed that the best experimental procedure involves cooling a solution of homoanhydride in CH_2Cl_2 to −78 °C before (+)-BTM **48** was added and the reaction stirred for 20 min. Next, a solution of 2-aroyl acrylate in CH_2Cl_2 is pre-cooled to −78 °C before being added to the reaction mixture. Finally, *i*-Pr_2NEt was added dropwise and the reaction stirred until complete by TLC analysis, with care being taken to maintain the reaction temperature at −78 °C.

4.2.2 Substrate Scope

To assess the generality of this reaction a range of 2-aroyl acrylates was prepared in acceptable overall yields (Table 18).

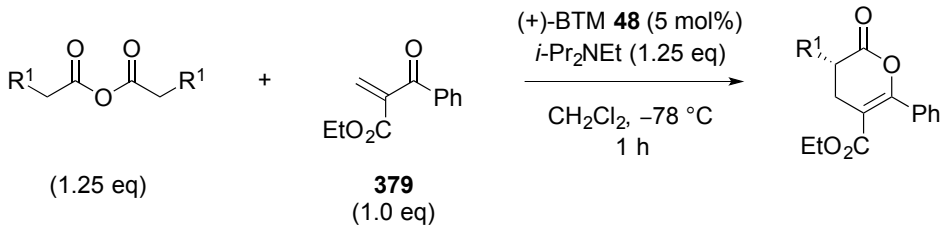


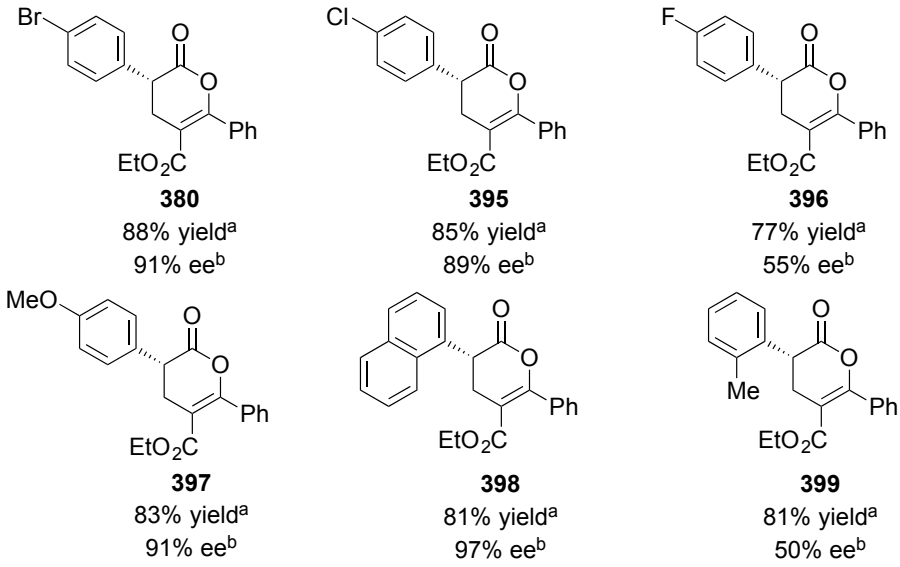
β-Keto esters				2-Aroyl acrylates			
Entry	**Compound No.**	**R^1**	**Yield (%)[a]**	**Entry**	**Compound No.**	**R^1**	**Yield (%)[a]**
1	**384**	4-$MeOC_6H_4$	75	**7**	**389**	4-$MeOC_6H_4$	89
2	**385**	4-MeC_6H_4	78	**8**	**390**	4-MeC_6H_4	61
3	**386**	2-furyl	49	**9**	**391**	2-furyl	48
4	**387**	3-BrC_6H_4	50	**10**	**392**	3-BrC_6H_4	21
5	**388**	2-Np	60	**11**	**393**	2-Np	50

[a]Isolated following column chromatography.

Table 18 - Synthesis of 2-aroyl acrylates.

With the optimum conditions for applying homoanhydrides and 2-aroylacrylates in enantioselective isothiourea-catalysed Michael addition-lactonisation established, the substrate scope was first assessed with variation in the homoanhydride (Table 19). The 4-Cl substituted phenyl substituent was incorporated at the 3-position of dihydropyranone **395** in 85% yield and 89% ee. 2-(4-Fluorophenyl)acetic anhydride provides product **396** in good 77% yield but disappointing 55% ee. Electron-rich 4-$MeOC_6H_4$ substitution, provided the corresponding dihydropyranone **397** in 83% yield and 91% ee. Pleasingly, the sterically demanding 2-(naphthalen-1-yl)acetic anhydride was applied successfully with **398** formed in excellent 81% yield and 97% ee. However, the sterically demanding 2-tolyl group was installed at the 3-position of **399** in good 81% yield, but with moderate 50% ee.





[a]Isolated following column chromatography using Biotage® Isolera™ 4. [b]Determined by chiral HPLC.

Table 19 - Substrate scope: variation of homoanhydride.

The absolute configuration at the C(1) and C(2) position of **398** was confirmed by X-ray crystallography to be (3*R*). All other dihydropyranones were assigned by analogy.

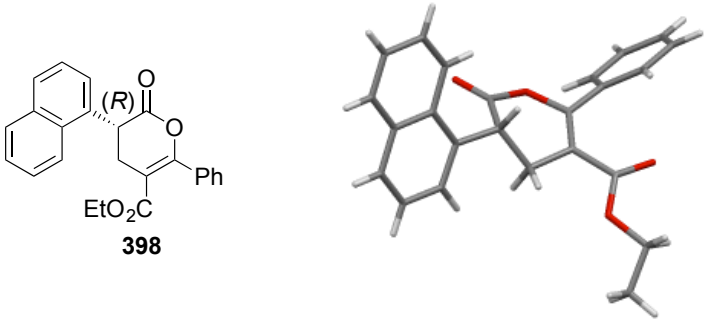
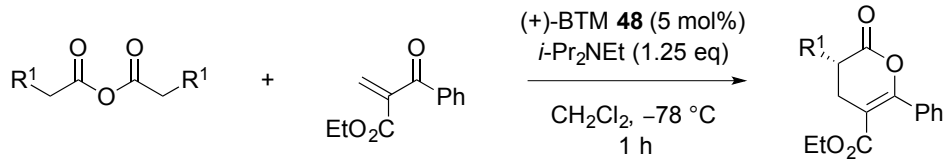
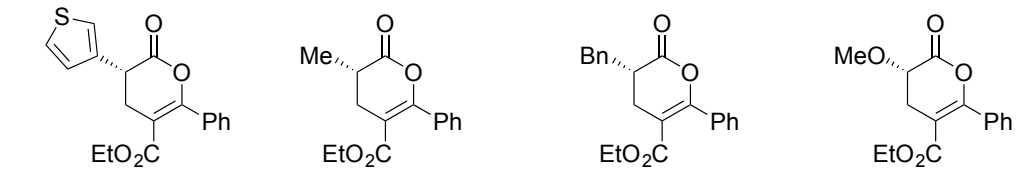


Figure 31 - X-ray crystal structure and molecular representation of (3*R*)-398.

A number of examples proved problematic within this methodology (Table 20). 3-Thienyl dihydropyranone **400** could be synthesised in 71% yield, but with no enantioselectivity. In an attempt to extend the scope beyond aryl homoanhydrides, propionic anhydride and 3-phenylpropanoic anhydride were examined. It was predicted that these substrates would require a stronger base to facilitate the deprotonation of the ammonium enolate as had been discovered in related systems.[97] Using PS-BEMP as the reaction base unfortunately did not show any conversion into the corresponding dihydropyranones **401** and **402**. 2-Methoxyacetic anhydride

was next investigated, but also gave no conversion into **403** using either *i*-Pr_2NEt or PS-BEMP applied as the reaction base. Indolyl, phenylthio, propenyl and phenylpropenyl examples **404-407** showed full conversion into product in all cases (as determined by ^1H NMR spectroscopy) but proved difficult to isolate due to a lack of stability towards column chromatography.



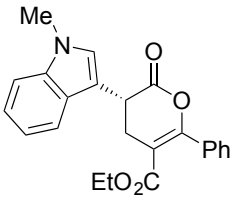


400
71% yield[a]
0% ee[b]

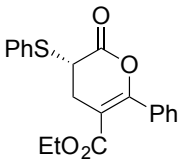
401[c]
No observable conversion

402[a]
No observable conversion

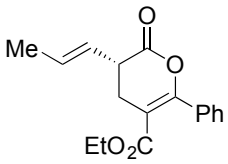
403[c]
No observable conversion



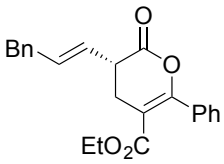
404
Unstable to column chromatography



405
Unstable to column chromatography



406
Unstable to column chromatography

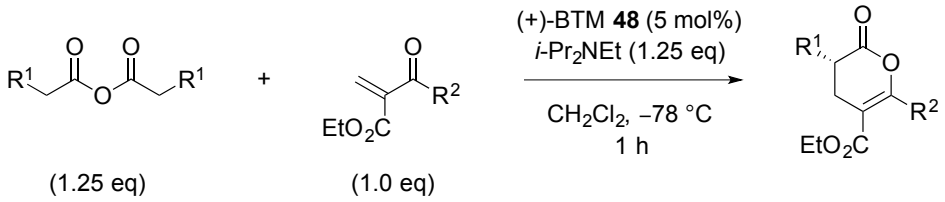


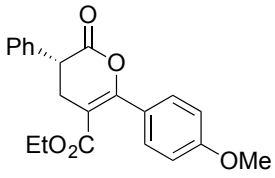
407
Unstable to column chromatography

[a]Isolated following column chromatography using Biotage® Isolera™ 4. [b]Determined by chiral HPLC. [c]PS-BEMP (1.25 eq) applied as reaction base.

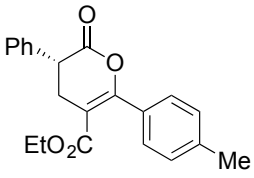
Table 20 – Substrate scope: unsuccessful dihydropyranone examples.

Variation of the 2-aroyl acrylate Michael acceptor was next investigated (Table 21). Electron-rich substituents were tolerated at the 6-position giving 4-$MeOC_6H_4$ and 4-tolyl examples **408** and **409** in excellent 79% and 65% yield with 91% and 81% ee, respectively. Interestingly in the case of **409**, the reaction with *i*-Pr_2NEt gave the product in 0% ee but changing the reaction base to Na_2CO_3 provided **409** in improved 81% ee. In other instances where enantioselectivities were low using Na_2CO_3 as the base did not show any improvement. Three Michael acceptors, proved unsuccessful when employing phenylacetic anhydride giving the desired products **410**, **412** and **414** in good yields but with 0% ee. Employing 4-methoxyphenylacetic anhydride in these reactions gave the corresponding products **411, 413** and **415** in good yield and with improved good to excellent levels of enantioselectivity.

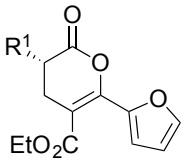




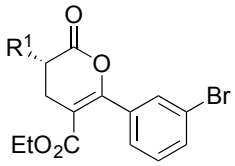
408
79% yield[a]
91% ee[b]



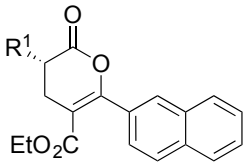
409
65% yield[a]
81% ee[b,c]



R^1 = Ph, **410**,
64% yield[a], 0% ee[b]
4-$MeOC_6H_4$, **411**,
61% yield[a], 99% ee[b]



R^1 = Ph, **412**,
66% yield[a], 0% ee[b]
4-$MeOC_6H_4$, **413**,
61% yield[a], 68% ee[b]



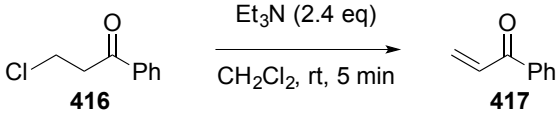
R^1 = Ph, **414**,
75% yield[a], 0% ee[b]
4-$MeOC_6H_4$, **415**,
61% yield[a], 86% ee[b]

[a]Isolated following column chromatography using Biotage® Isolera™ 4. [b]Determined by chiral HPLC. [c]Na_2CO_3 (1.25 eq) applied as reaction base.

Table 21 - Substrate scope: variation of 2-aroyl acrylate.

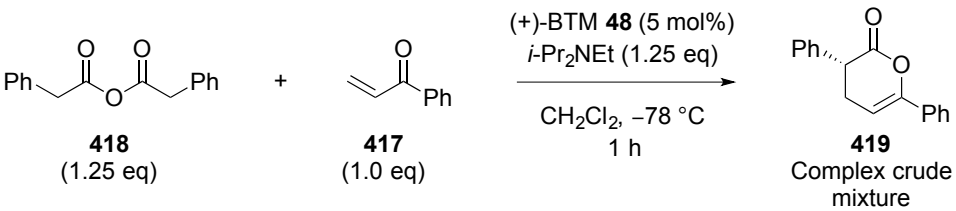
To evaluate this methodology for the synthesis of 3,6-substituted dihydropyranones, Michael acceptor **417** was prepared using the procedure from Iwasa and co-workers.[98] Treatment of 3-chloropropiophenone **416** with Et_3N in CH_2Cl_2 at rt produces 1-phenylprop-2-en-1-one **417** in quantitative yield (Scheme 74a). Due to the instability of **417**, this was submitted to the optimum conditions immediately but led to complete decomposition with no observation of the desired product **419** (Scheme 74b).

a.) Synthesis of 1-phenylprop-2-en-1-one 417



416 → **417**
Quant.

b.) Reactivity of 1-phenylprop-2-en-1-one 417



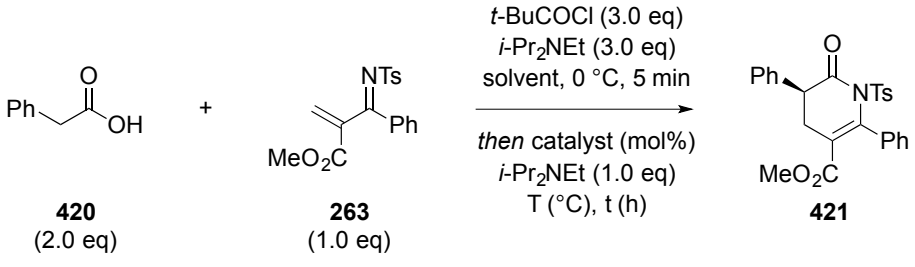
418 (1.25 eq) + **417** (1.0 eq) → **419**
Complex crude mixture

Scheme 74 - Synthesis and reactivity of 1-phenylprop-2-en-1-one 417.

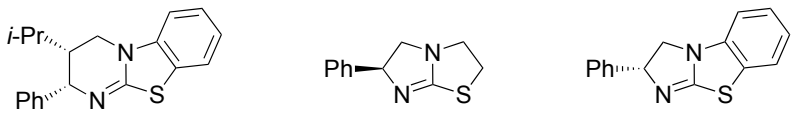
4.3 Michael Addition-Lactamisation

4.3.1 Initial Results and Reaction Optimisation

Following the successful synthesis of dihydropyranones through an isothiourea-catalysed Michael addition-lactonisation process, the synthesis of structurally related 2,3,5-substituted dihydropyridinones was explored. Studies were initiated with a reaction optimisation applying 2-*N*-tosyliminoacrylate **263** and phenylacetic acid **420**. Reaction of **420**, pivaloyl chloride and *i*-Pr_2NEt followed by addition of Michael acceptor **263** and (2*S*,3*R*)-HyperBTM **53** (10 mol%) in CH_2Cl_2 at room temperature gave dihydropyridinone (*ent*)-**421** in 60% yield and 80% ee (Table 22). Next, a screen of isothiourea catalysts was undertaken with (+)-BTM **48** providing (*ent*)-**421** in 60% yield and 80% ee and (−)-tetramisole•HCl **47** gave **421** in 62% yield and 84% ee. With moderate enantioselectivities observed at room temperature, the reaction temperature was lowered to −78 °C and the catalysts **53**, **47** and **48** examined. (2*S*,3*R*)-HyperBTM **53** and (+)-BTM **48** showed slightly improved 86% and 85% ee, respectively, however (−)-tetramisole•HCl **47** proved optimal giving **421** in 74% yield and 91% ee. Changing the reaction solvent to THF gave **421** in reduced 40% yield and 86% ee. Interestingly, conducting the reaction in MeCN gave **421** with no enantioselectivity. Finally, the limit of the catalyst loading was probed with maintenance of the good yield and enantioselectivity observed with 5 mol% **47**, but a poor 50% conversion into **47** using 2 mol%.



420 (2.0 eq) **263** (1.0 eq) **421**



(2*S*,3*R*)-HyperBTM **53** (−)-Tetramisole•HCl **47** (+)-BTM **48**

Entry	Catalyst (mol%)	T (°C)	t (h)	Solvent	Yield (%)[a]	ee (%)[b]
1[c]	**53** (10)	rt	16	CH_2Cl_2	–[d]	–[d]
2	**53** (10)	rt	0.5	CH_2Cl_2	60	(ent) 80[e]
3	**47** (10)	rt	0.5	CH_2Cl_2	62	84
4	**48** (10)	rt	0.5	CH_2Cl_2	60	(ent) 80[e]

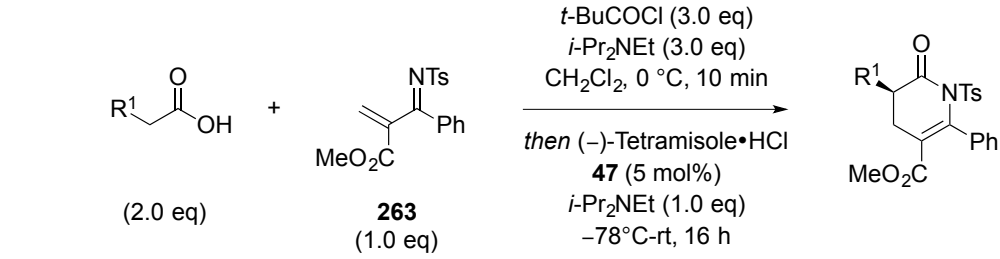
5	**53** (10)	−78	16	CH_2Cl_2	71	(*ent*) 86[e]
6	**47** (10)	−78	16	CH_2Cl_2	74	91
7	**48** (10)	−78	16	CH_2Cl_2	70	(*ent*) 85[e]
8	**47** (10)	−78	16	THF	40	86
9	**47** (10)	−78	16	MeCN	70	0
10	**47** (5)	−78	16	CH_2Cl_2	74	91
11	**47** (2)	−78	16	CH_2Cl_2	–[f]	–[d]

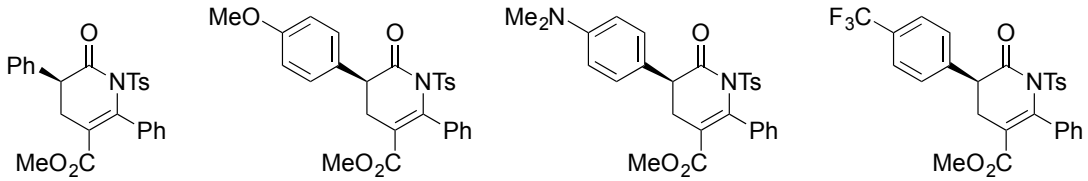
[a]Isolated following column chromatography. [b]Determined by chiral HPLC analysis. [c] Using 1.0 eq of **420** only 58% conversion was obtained (determined by ^{1}H NMR spectroscopy). [d]Not determined. [e](*R*)-enantiomer obtained. [e](*R*)-enantiomer obtained. [f]50% conversion (determined by ^{1}H NMR spectroscopy).

Table 22 – Michael addition-lactamisation reaction optimisation.

4.3.2 Substrate Scope

Moving onto the substrate scope, many examples gave poor conversion at −78 °C and so a modified system allowing the reaction to warm to room temperature over 16 h was used as a more general procedure. The generality was first probed with a range of acetic acids and Michael acceptor **263** (Table 23). Electron-rich aromatics 4-$MeOC_6H_4$ and 4-$Me_2NC_6H_4$ were well tolerated, giving products **422** and **423** in 76% and 71% yield with excellent 95% and 94% ee, respectively. Electron-deficient CF_3-substituted phenyl substituent was installed at the 5-position giving **424** in 74% yield and 91% ee. Heteroaryl substituent, 2-thienyl dihydropyridinone **425** was achieved in 65% yield and 90% ee. 3-Tolyl acetic acid worked well with product **426** produced in 69% yield and 95% ee. Application of 4-bromophenylacetic acid gave the corresponding dihydropyridinone **427** in good 61% yield but in moderate 71% ee. This drop in enantioselectivity is likely due to strong competition from a base-promoted racemic background reaction. 4-Bromophenyl acetic anhydride was tested in hope that enhanced enantioselectivity would be achieved, as discovered with 2-aroyl acrylates, but this showed no improvements with a moderate 70% ee attained.



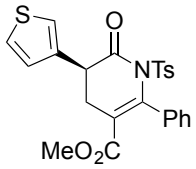


421
74% yield[a]
91% ee[b]

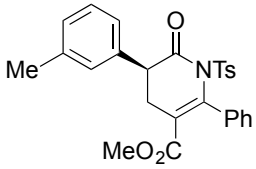
422
76% yield[a]
95% ee[b]

423
71% yield[a]
94% ee[b]

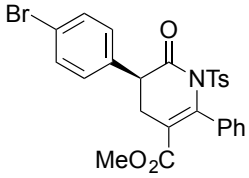
424
74% yield[a]
91% ee[b]



425
65% yield[a]
90% ee[b]



426
69% yield[a]
95% ee[b]

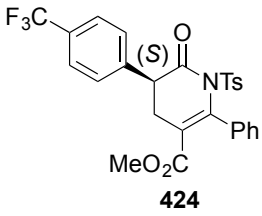


427
61% yield[a]
71% ee[b]

[a]Isolated following column chromatography. [b]Determined by chiral HPLC.

Table 23 - Michael addition-lactamisation scope: variation of acetic acid.

The absolute configuration at the C(5) position of **424** was confirmed by X-ray crystallography to be (*S*). All other dihydropyridinones were assigned by analogy.



424

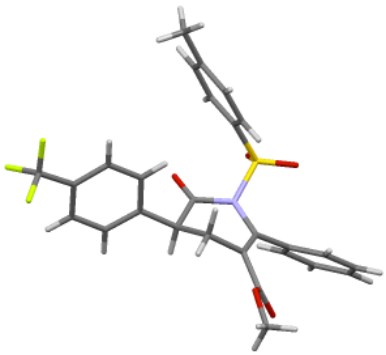
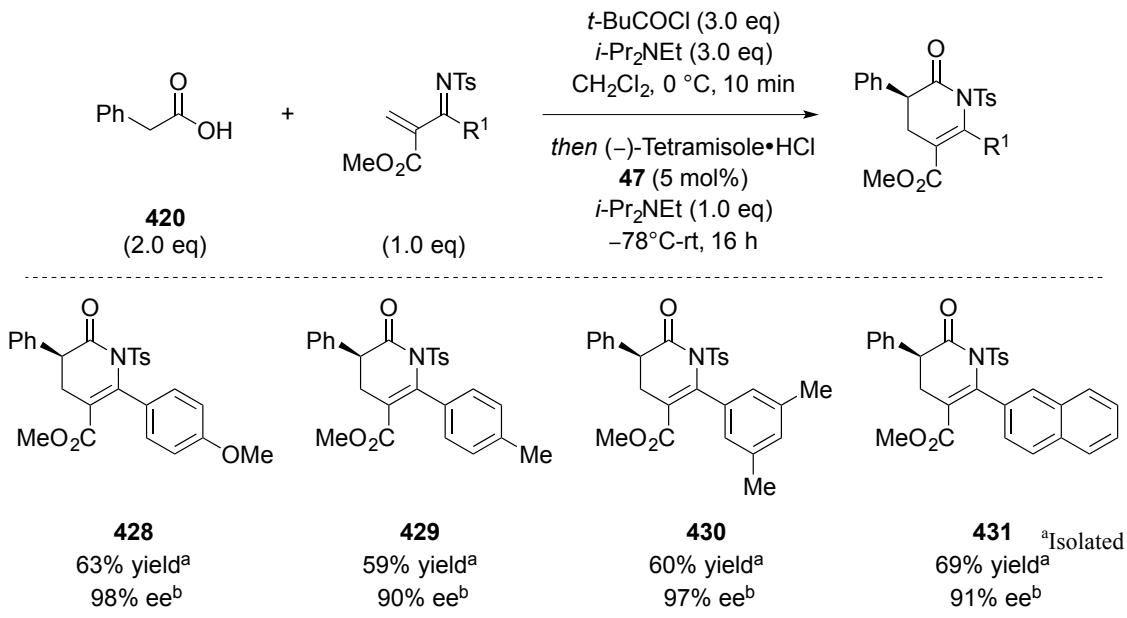


Figure 32 - X-ray crystal structure and molecular representation of (5*S*)-424.

A range of 2-*N*-tosyliminoacrylates, prepared as in chapter 3, were next assessed in the scope of this enantioselective Michael addition-lactamisation. The 4-$MeOC_6H_4$ containing Michael acceptor **267** is tolerated giving dihydropyridinone **428** in 63% yield and excellent 98% ee. Methyl substituted phenyl rings 4-tolyl and 3,5-xylyl could be successfully incorporated at the 2-position to provide dihydropyridinones **429** and **430** in 59% and 60% yield and 90% and

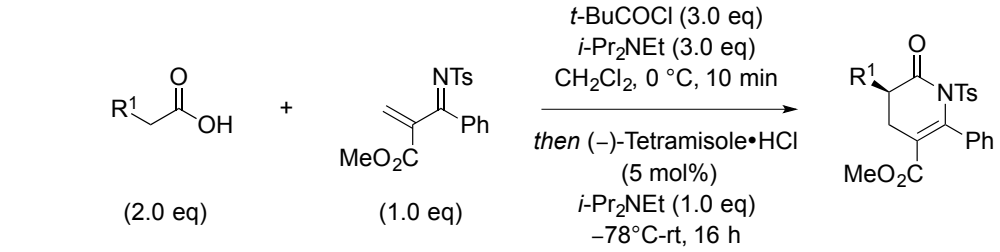
97% ee, respectively. Finally, 2-Np ketimine **289** was applied to produce **431** in good 69% yield and 91% ee.

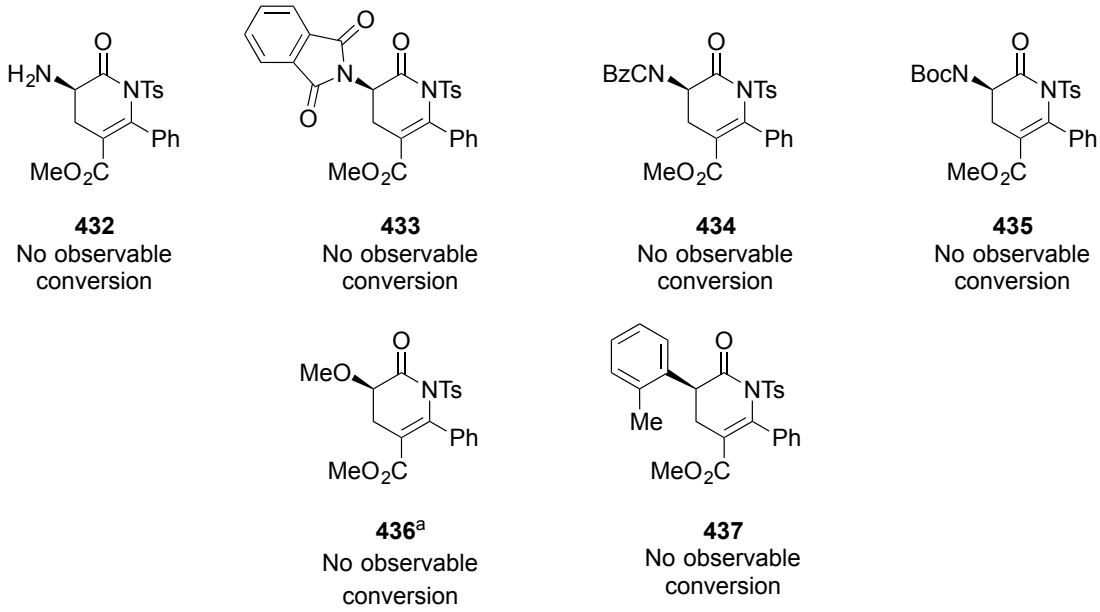


[a]Isolated following column chromatography. [b]Determined by chiral HPLC.

Table 24 - Michael addition-lactamisation scope: variation of 2-*N*-tosyliminoacrylate.

Given the success of the isothiourea-catalysed Michael addition-lactamisation protocol, some more challenging enolate precursors and Michael acceptors were investigated. Functionalisation of amino acids was attempted with the use of glycine and *N*-protected glycine derivatives (Table 25). Unfortunately, no conversion into desired dihydropyridinones **432-437** was obtained (determined by ^{1}H NMR spectroscopy). Methoxyacetic acid was probed using PS-BEMP as the reaction base, but gave no conversion into product **436**. 2-Tolyl acetic acid also proved unsuccessful, most likely due to the steric demand of the 2-substituted aryl acetic acid.





432
No observable conversion

433
No observable conversion

434
No observable conversion

435
No observable conversion

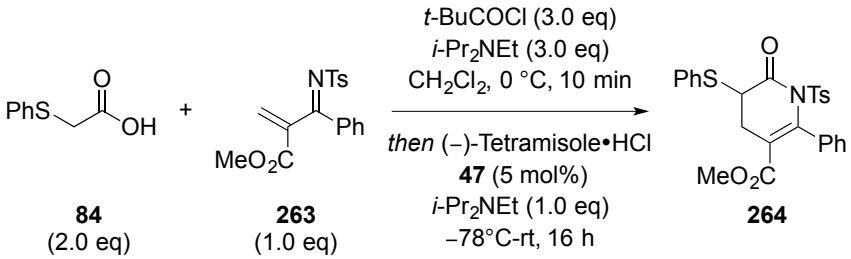
436[a]
No observable conversion

437
No observable conversion

[a]PS-BEMP (1.25 eq) used as reaction base.

Table 25 - Michael addition-lactamisation scope: unsuccessful examples.

(Phenylthio)acetic acid **84** was previously applied to the racemic Michael addition-lactamisation applied in the synthesis of pyridine sulfonates (Chapter 2 and 3). Interestingly, applying **84** in the enantioselective protocol gave racemic dihydropyridinone **264** in 65% yield (Scheme 75). To test if this was due to epimerisation or a competitive racemic background reaction, the control reaction in the absence of a Lewis base catalysis was conducted and did not provide any observable conversion into **264**. This suggests that the C(5)−H pK_a is low enough to undergo an epimerisation to give the racemic product. This also provides indirect evidence towards a feasible epimerisation mechanism of PhSH elimination discussed in Chapter 2 in the one-pot synthesis of pyridines.



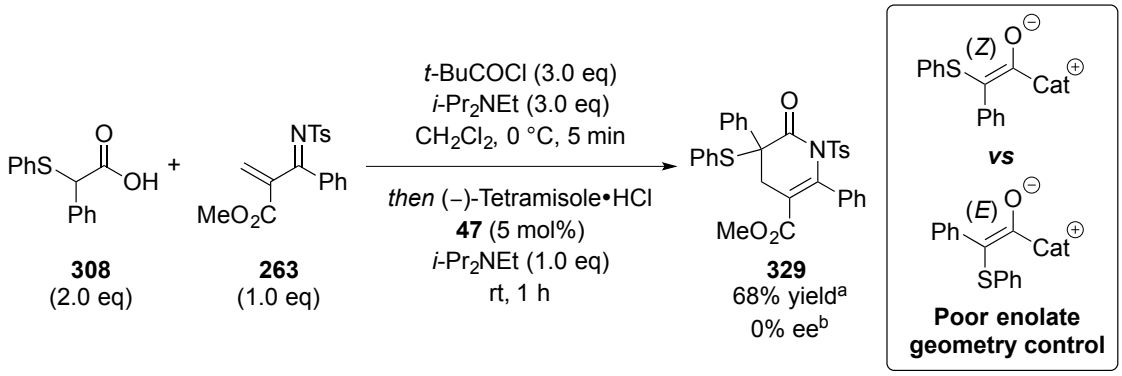
(–)-Tetramisole•HCl:
65% yield[a], 0% ee[b]

No Lewis base:
No observable conversion

[a]Isolated following column chromatography. [b]Determined by chiral HPLC.

Scheme 75 - Application of (phenylthio)acetic acid 84.

Following the application of α,α–disubstituted acetic acids in chapter 3, a particularly interesting example was that of applying (phenylthio)phenyl acetic acid **308** in the enantioselective process. The reaction provides **329** in good 68% yield but with no enantioselectivity (Scheme 76). As there is no major racemic background reaction in the Michael addition-lactamisation protocol, the absence of enantioselectivity could be due to poor control over the (*E*)- and (*Z*)-enolate geometries formed in the reaction.



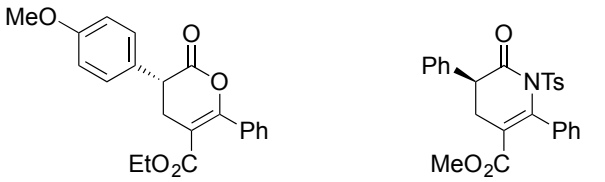
308 (2.0 eq) + **263** (1.0 eq) → **329** 68% yield[a] 0% ee[b]

[a]Isolated following column chromatography. [b]Determined by chiral HPLC.

Scheme 76 - Application of (phenylthio)phenyl acetic acid 308.

4.4 Derivatisations

To explore the synthetic utility of the dihydropyranones and dihydropyridinones produced in the enantioselective isothiourea-catalysis process developed herein, **397** and **421** were prepared on a gram-scale and a range of derivatisations attempted.



397 (4.27 mmol scale) 1.27 g, 84% yield[a] 87% ee[b]

421 (4.17 mmol scale) 1.33 g, 69% yield[a] 99% ee[b]

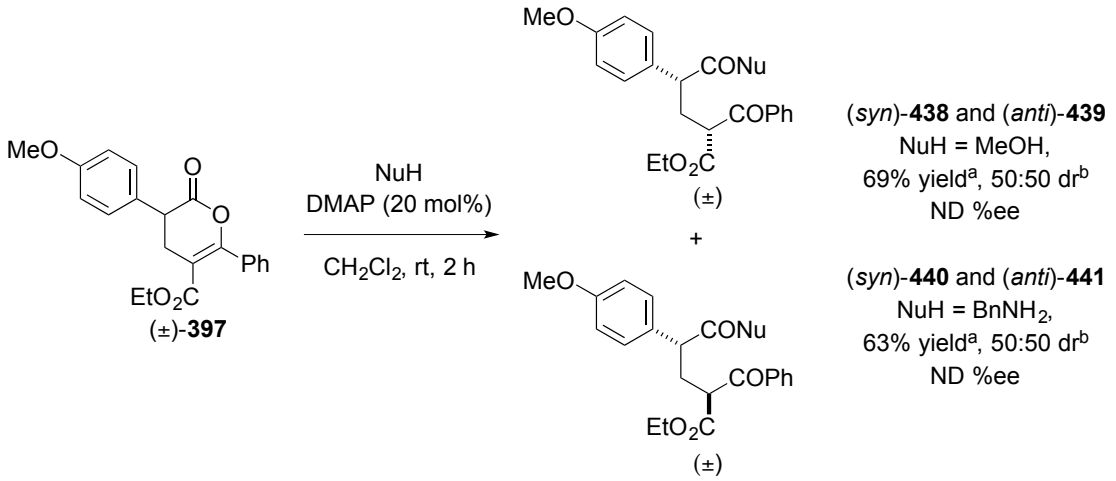
[a]Isolated following column chromatography. [b]Determined by chiral HPLC.

Figure 33 - Scaled-up synthesis of (3*R*)-397 and (5*S*)-421.

4.4.1 Dihydropyranone Derivatisation

The first dihydropyranone transformation attempted was the ring opening of (±)-**397** with either MeOH or $BnNH_2$ in the presence of sub-stoichiometric DMAP (Scheme 77). It was predicted that a 50:50 mixture of diastereoisomers would be produced with no control over the new stereocentre at C(2). However, it was hoped that these diastereoisomers would be separable

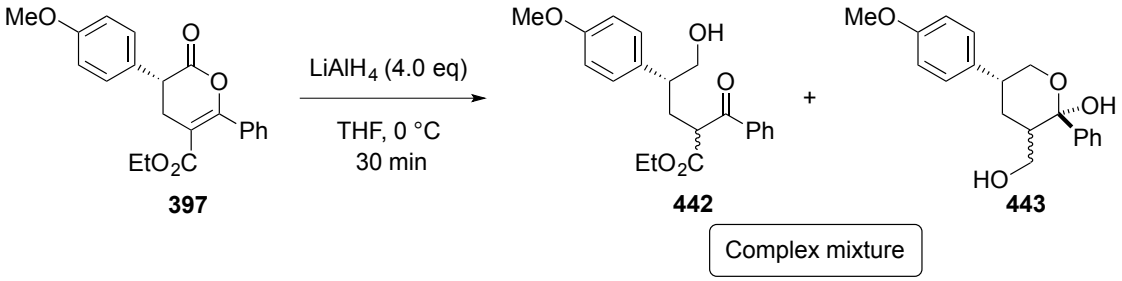
and hence provide a stereodivergent process, overall. In both examples the diastereoisomers were not separable by column chromatography and were therefore not pursued any further.



[a]Isolated following column chromatography.[b]Determined by ^{1}H NMR spectroscopy.

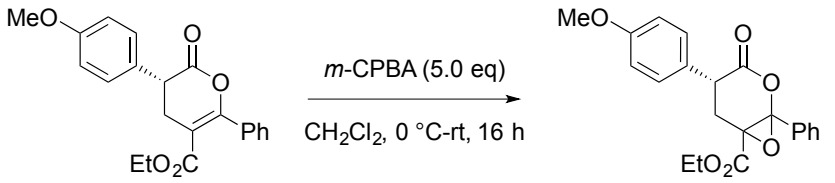
Scheme 77 - Ring opening of (±)-397.

An alternative ring opening using $LiAlH_4$ was investigated (Scheme 78). Following full consumption of **397** a complex mixture of products was obtained (as determined by ^{1}H NMR spectroscopy). From the ^{1}H NMR analysis, it's believed that this complex mixture consisted of the desired alcohol **442**, ring closed lactol **443**, known to form under these conditions in related systems,[42] with other products produced from decomposition. Efforts to isolate these products were unsuccessful.



Scheme 78 - Attempted reductive ring opening of (3*S*)-397.

The first attempt to utilise the olefin component of **397** was an *m*-CPBA epoxidation, with 30% conversion into epoxide **444** after 16 h was determined by ^{1}H NMR spectroscopy (Scheme 79). However, product **444** underwent decomposition upon work-up or attempted purification.



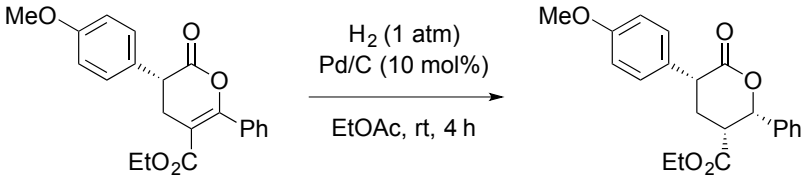
397 **444**

30% conversion[a]

[a]Determined by ^{1}H NMR spectroscopy.

Scheme 79 - Attempted epoxidation of (3*S*)-397.

Pleasingly, the Pd/C catalysed hydrogenation of **397** under one atmosphere of hydrogen gave pyranone **445** in 60% yield and >95:5 dr (Scheme 80).



397 **445**

60% yield[a]

>95:5 dr[b]

[a]Isolated following column chromatography.[b]Determined by ^{1}H NMR spectroscopy.

Scheme 80 - Hydrogenation of 397.

Unambiguous determination of the product enantioselectivity proved difficult, with **445** decomposing under both chiral HPLC and GC analysis. To examine the relative configuration within pyranone **445**, ^{1}H NMR spectroscopy was utilised (Figure 34). Firstly, NOESY experiments with irradiation at the C(6) position confirmed the relative configuration to be *syn* with positive NOE signals for C(3)*H* and C(5)*H*. Coupling constant signal analysis for C(5)*H* confirms the *syn*-configuration at C(5) and C(6) with the ddd signal at 3.39 ppm. This analysis shows an axial-equatorial $^3J_{HH}$ coupling constant of 4.5 Hz between C(5)H_{ax} and C(5)H_{eq}. Coupling to the C(4)H_{ax} and C(4)H_{eq} is also observed with $^3J_{HH}$ coupling constants of 8.2 Hz and 5.9 Hz, respectively.This supports a stereoselective hydrogenation with hydrogen adding to the *Re*-face opposite to that of the substituent at C(3). Given the high 87% ee observed for **397** and the the high >95:5 *syn*-diastereoselectivity observed for **445**, it can be suggested that pyranone **445** was prepared as the (2*S*,3*R*,5*R*)-stereoisomer.

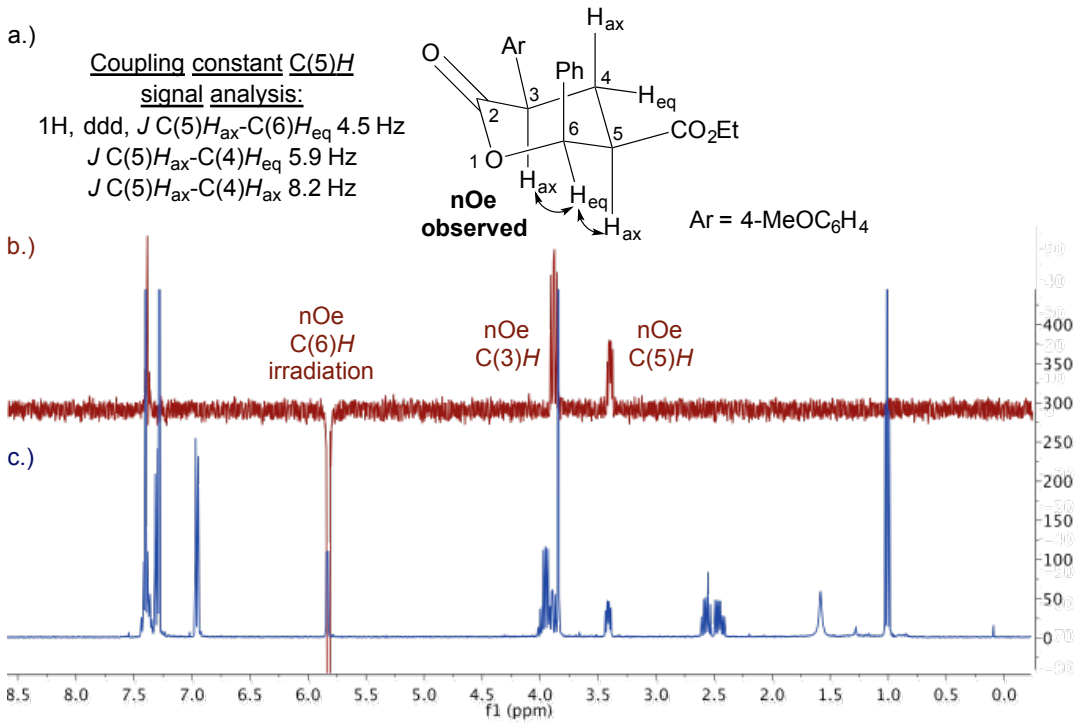
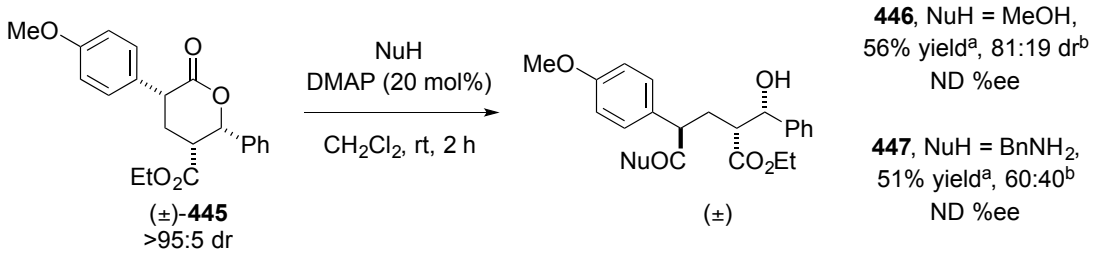


Figure 34 - a.) Coupling constant analysis of C(5)*H*. b.) 1D gs-NOESY spectrum of 445 with irradiation at C(6). c.) ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 445.

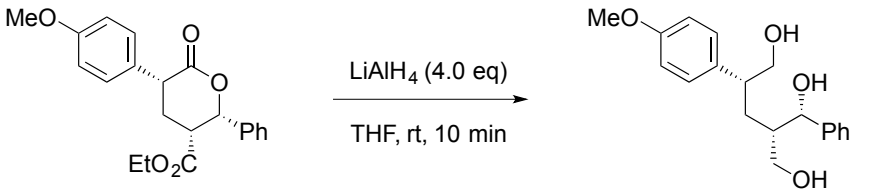
With (±)-**445** in hand, a number of ring openings were explored. Using sub-stoichiometric DMAP and either MeOH or benzylamine as the nucleophile, products (±)-**446** and (±)-**447** were obtained in moderate to poor dr (81:19 and 60:40, respectively) (Scheme 81). As (±)-**397** was submitted to the reactions as a single diastereoisomer this result implies that an epimerisation has taken place at a stereocentre under the reaction conditions. Therefore, these ring openings were not pursued further.



[a]Isolated following column chromatography. [b]Determined by ^{1}H NMR spectroscopy.

Scheme 81 - Attempted ring opening of (±)-397 with MeOH or $BnNH_2$.

A reductive ring opening with $LiAlH_4$ provided triol (1*S*,2*S*,4*R*)-**448** in excellent 88% yield from (2*S*,3*R*,5*R*)-**445** with no loss of diastereoselectivity (Scheme 82). This compound proved challenging to determine the enantioselectivity, with decomposition observed in both chiral HPLC and GC. Nonetheless, the stereochemistry was assigned by analogy with the enantiomer produced in the synthesis of (3*R*)-**397** and subsequent *syn*-selective hydrogenation to (2*S*,3*R*,5*R*)-**445**.



445
>95:5 dr

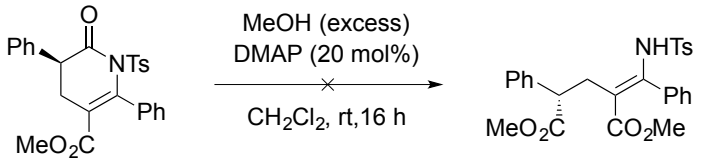
448
88% yield[a]
ND %ee, >95:5 dr[b]

[a]Isolated following column chromatography. [b]Determined by ^{1}H NMR spectroscopy.

Scheme 82 - Reductive ring opening of (2*S*,3*R*,5*R*)-397.

4.4.2 Dihydropyridinone Derivatisation

Dihydropyridinone **421** proved difficult to ring open with nucleophiles. Reaction using excess MeOH and substoichiometric DMAP with **421** gave no conversion with starting materials returned (Scheme 83).

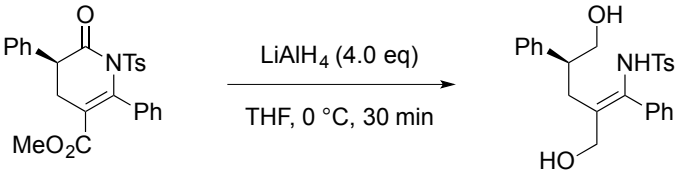


421

449
No observable conversion

Scheme 83 - Attempted methanolic ring opening of 421.

Dihydropyridinone **421** was treated with $LiAlH_4$ in an attempt to produce diol **450** (Scheme 84). Full consumption of **421** was observed but a complex mixture of products was obtained. Endeavours to isolate the components of the crude mixture were unsuccessful.

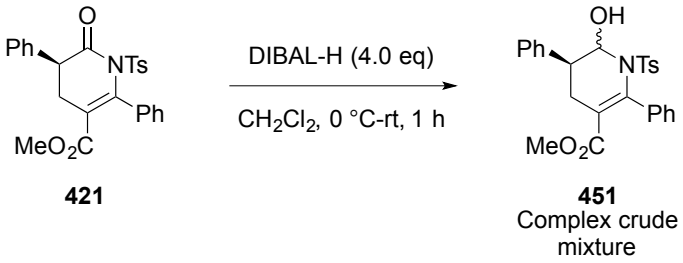


421

450
Complex crude mixture

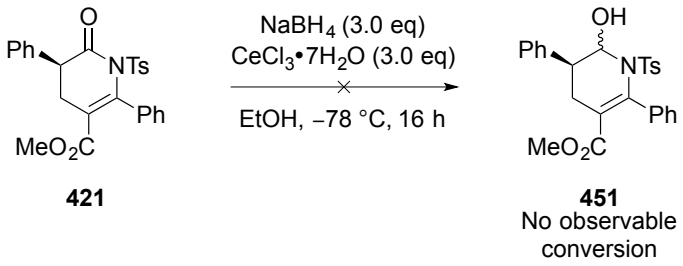
Scheme 84 - Attempted reductive ring opening of 421.

Hemiaminals derived from dihydropyridinones are useful synthetic building blocks, in particular for the synthesis of functionalised piperidines.[99] It was therefore intended to produce hemiaminal **451** from reduction of **421** using DIBAL-H, however a complex mixture of what was determined (by ^{1}H NMR spectroscopy) to be mostly decomposition material was obtained (Scheme 85).



Scheme 85 - Attempted reduction of 421 into hemianminal 451.

Applying the procedure outlined by Sakamoto and co-workers a milder Luche reduction with $NaBH_4$ and $CeCl_3 \bullet 7H_2O$ was attempted, but in this case only starting materials were returned with no observable conversion into hemiaminal **451** (Scheme 86).



Scheme 86 - Attempted Luche reduction of (5*S*)-421.

4.5 Proposed Mechanism and Stereochemical Rationale

Following our previous studies a proposed mechanism for the processes described in this chapter begins with *N*-acylation of isothiourea catalyst with either the homoanhydride (with aroyl acrylates) or *in situ* formed mixed anhydride (with imino acrylates) to form an acyl ammonium species **453** (Figure 35). Subsequent deprotonation gives the (*Z*)-ammonium enolate **454**, which undergoes an enantioselective Michael addition to an aroyl acrylate or imino acrylate. Finally, lactamisation or lactonisation provides the corresponding heterocyclic products **457** and releases the catalyst.

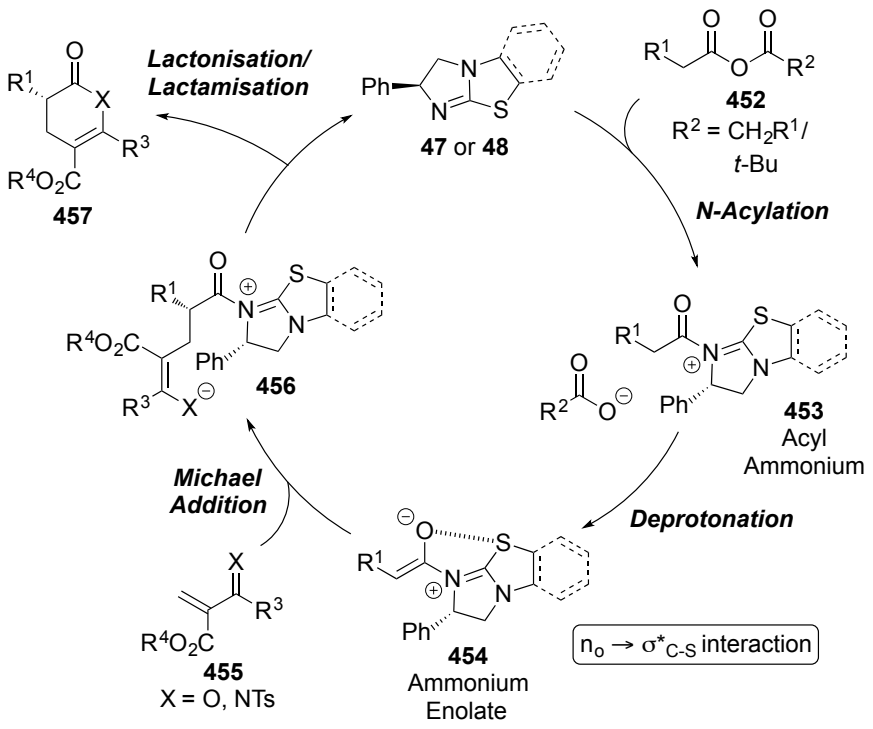


Figure 35 - Proposed mechanism of isothiourea-catalysed Michael addition-lactonisation/lactamisation.

Rationalisation of the observed enantioselectivity in the Michael addition-lactonisation reaction can be based upon the results and computational modelling of related systems (Figure 36).[100] Ammonium enolate forms with a (*Z*)-configuration, stabilised by either an enolate oxygen and the C−S *anti*-bonding orbital (n_o to σ^*_{C-S}) interaction or a favourable electrostatic interaction.[36-37, 101] This interaction is believed to rigidify **458** with the Ph directing group from catalyst **48** adopting a pseudo-axial orientation and blocking one face of the ammonium enolate. Inputting 2-aroyl acrylate **460** into this model, the next stage is the enantiodetermining Michael addition that can be assigned by analogy to the Heathcock model giving **462**.[102] Lactonisation turns over the catalyst and provides dihydropyranone (3*R*)-**463**. As the Michael addition-lactamisation process uses (−)-Tetramisole•HCl **47**, the pseudoenantiomer of (+)-BTM **48**, the stereochemical rationale is proposed to be the same but the mirror image giving (5*S*)-**463**.

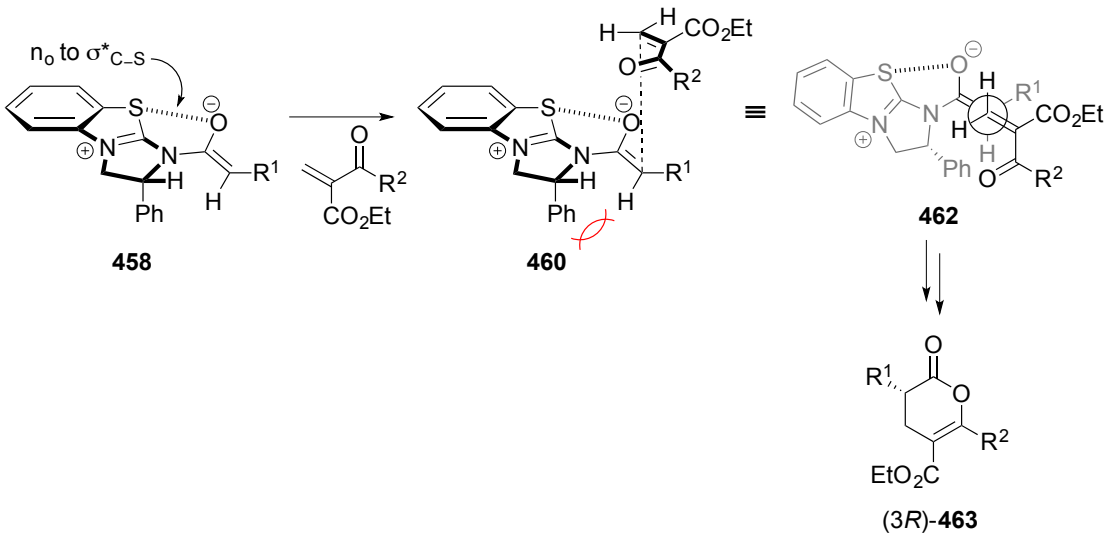


Figure 36 - Proposed stereochemical rationale.

4.6 Conclusions

In conclusion, it has been shown that isothiourea-catalysed Michael addition-lactamisation/lactonisation of either 2-aroyl acrylates or 2-imino acrylates with homoanhydrides or arylacetic acids, respectively, produces 3,5,6-substituted dihydropyranones and dihydropyridinones. Reaction yields and enantioselectivities are typically excellent in both protocols. Derivatisation of the products through hydrogenation and ring opening processes has demonstrated the use of these products as chiral building blocks.

4.7 References and Notes

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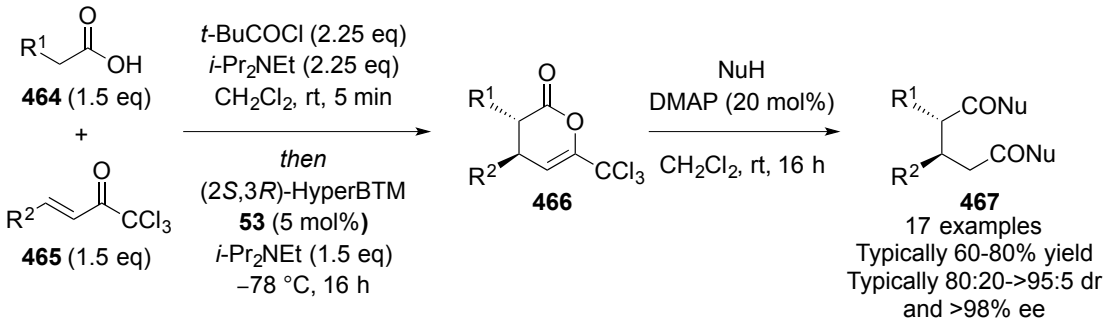
[102] For an overview of this area see: a) D. A. Oare, C. H. Heathcock, *Topics Stereochem*. **1989**, *19*, 227-407; For representative examples of enolate additions to Michael acceptors see: b) C. H. Heathcock, M. A. Henderson, D. A. Oare, M. A. Sanner, *J. Org. Chem.* **1985**, *50*, 3019-3022; c) D. A. Oare, M. A. Henderson, M. A. Sanner, C. H. Heathcock, *J. Org. Chem*. **1990**, *55*, 132-157. d) M. Yamaguchi, M. Tsukamoto, S. Tanaka, I. Hirao, *Tetrahedron Lett*. **1984**, *25*, 5661-5664; For a computational investigation of intermolecular Michael reactions see: e) E. E. Kwan, D. A. Evans, *Org. Lett.* **2010**, *12*, 5124-5127.

Chapter 5: Michael Addition-Lactonisations using α,β-Unsaturated Trichloromethyl Ketones

Chapter 5: Michael Addition-Lactonisations using α,β-Unsaturated Trichloromethyl Ketones

This chapter describes the application of α,β-unsaturated trichloromethyl ketones **465** in an isothiourea-catalysed Michael addition-lactonisation process to give dihydropyranones **466** (Scheme 87). Generally, these heterocycles have been utilised with an *in situ* ring opening and substitution of the CCl_3 group to provide access to chiral diesters and diamides **467** in excellent yield (typically 60-80%), diastereo- and enantioselectivity (80:20->95:5 dr and typically >98% ee).[103]



Scheme 87 - Organocatalytic Michael addition-lactonisation using α,β-unsaturated trichloromethyl ketones.

5.1 Introduction

Enantioselective Michael addition to electron deficient alkenes is a fundamental C−C bond forming transformation in organic chemistry with modern day efforts directed towards enantioselective Michael addition reactions.[104] Consequently, this area has seen much attention in recent years, with numerous examples demonstrated already in this thesis. At the forefront of interest has remained the use of organocatalysis with the application of H-bonding catalysis,[105] ammonium[18, 31b] and azolium enolates[106] in combination with electron-deficient enones, enals and nitro olefins. Intriguingly, the activation and enantioselective Michael addition into α,β-unsaturated esters and amides has proved challenging due to the inherent decreased reactivity of these substrates.

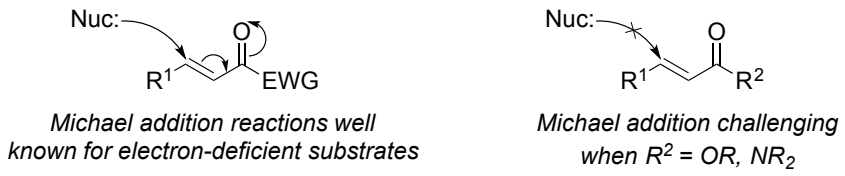


Figure 37 - General Michael acceptor reactivity observed in asymmetric catalysis.

To circumnavigate this problem a common strategy is the employment of activated ester surrogates as masked ester equivalents. Many of these examples are designed as ester/amide

surrogates capable of chelating chiral Lewis acid catalysts such as α,β-unsaturated *N*-acyl pyrroles,[107] *N*-acyl imidazoles,[108] or imides[109] (Figure 38).

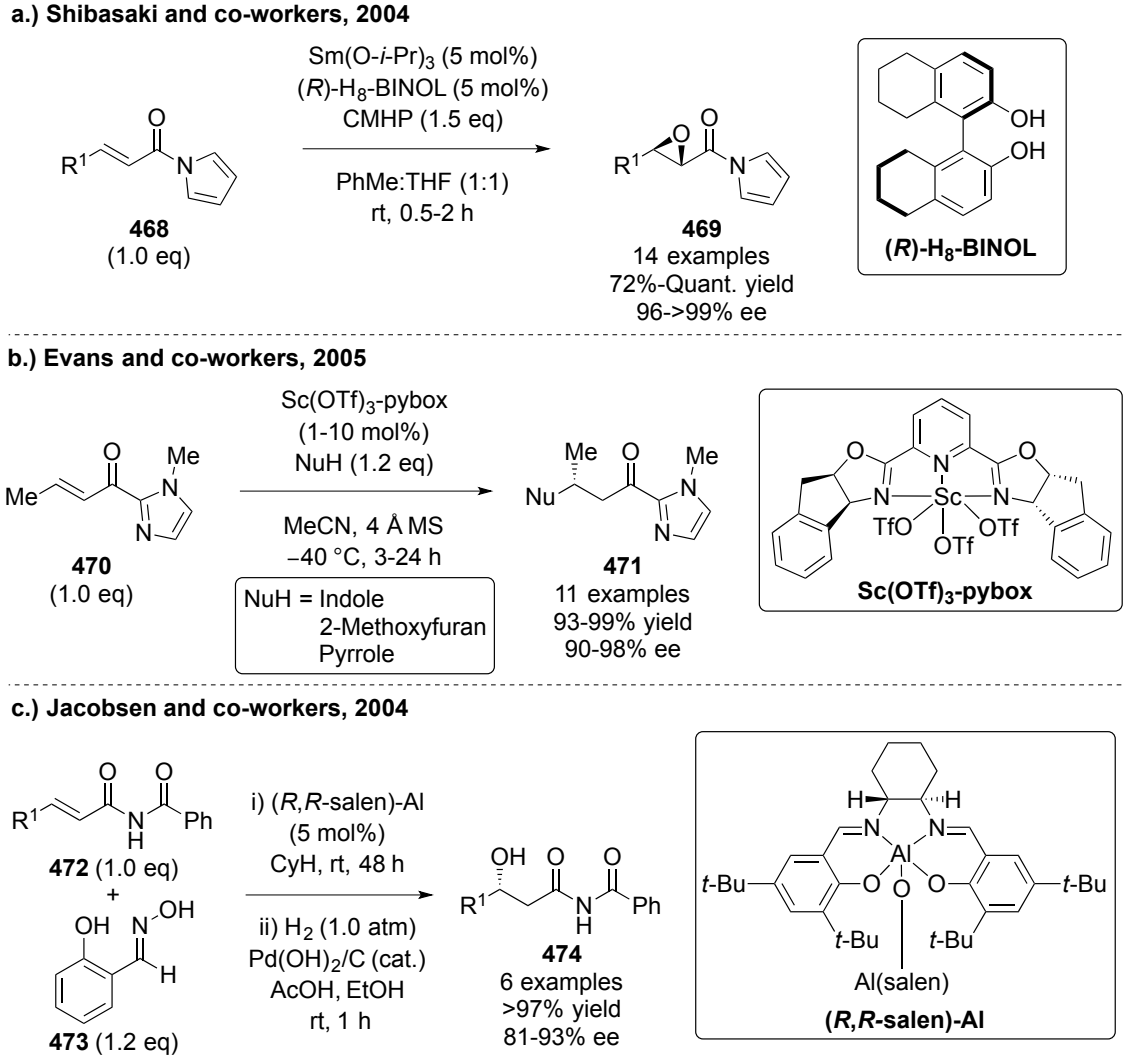
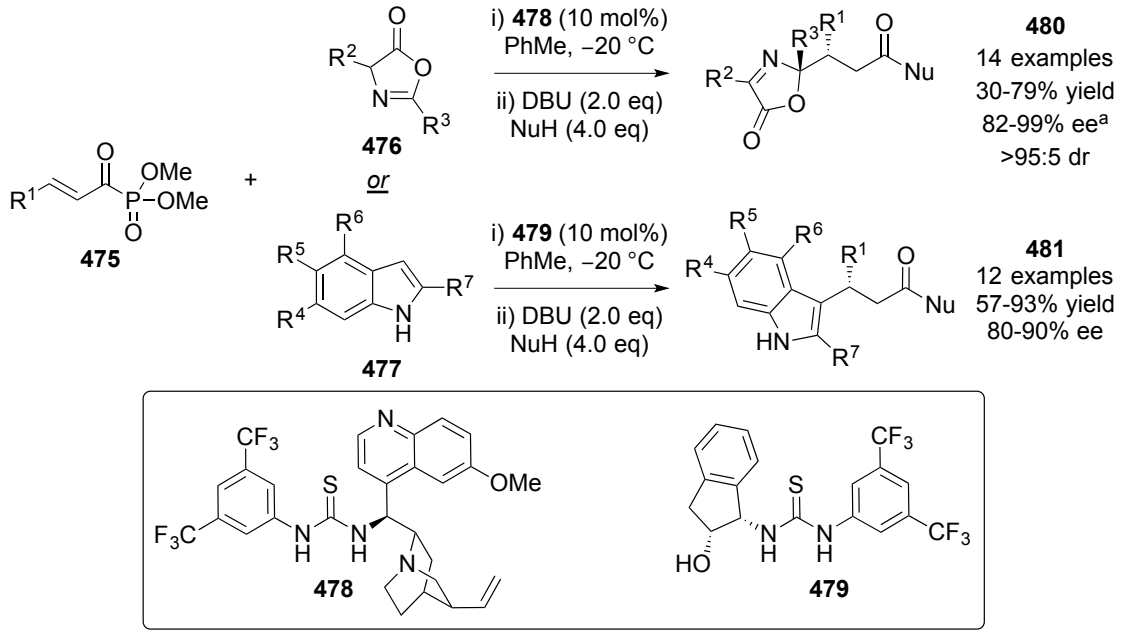


Figure 38 - Enantioselective Lewis acid-catalysed Michael addition strategies applying α,β-unsaturated ester/amide equivalents.

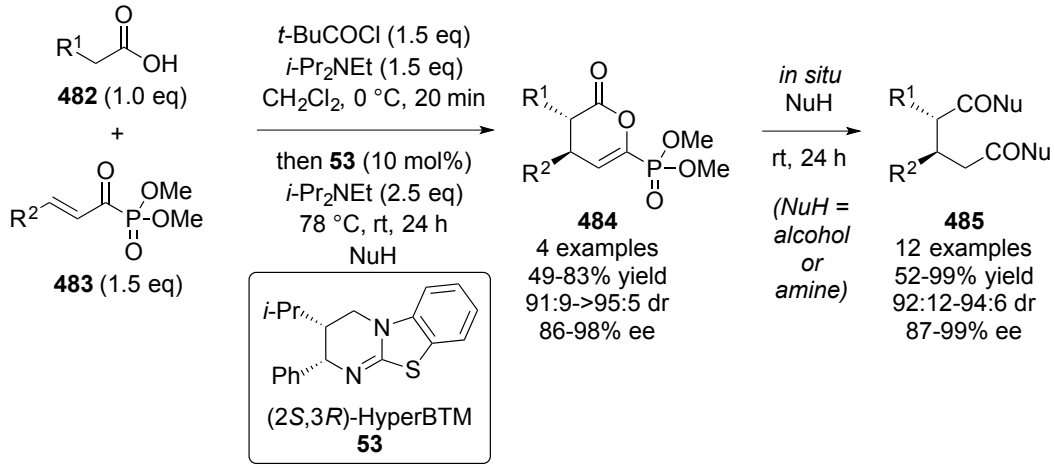
Phosphonates have also been used as ester/amide surrogates in Lewis acid-catalysed Michael addition reactions,[110] but more recently they have attracted interest within organocatalysis. Jørgensen and co-workers reported a pioneering example in 2010 using H-bonding catalysis (Scheme 88).[111] Treatment of unsaturated phosphonate **475** with thiourea **478** (10 mol%) and either oxazolone **476** or substituted indole **477** nucleophiles gives Michael addition adducts **480** and **481** in moderate to good yield and good to excellent enantioselectivity. In most cases the phosphonate group can be substituted *in situ* with a range of alcohols (e.g. MeOH, EtOH or BnOH) or amines (e.g. $BnNH_2$ or morpholine) thus producing the corresponding esters and amides.



[a]ee determined following recrystallisation.

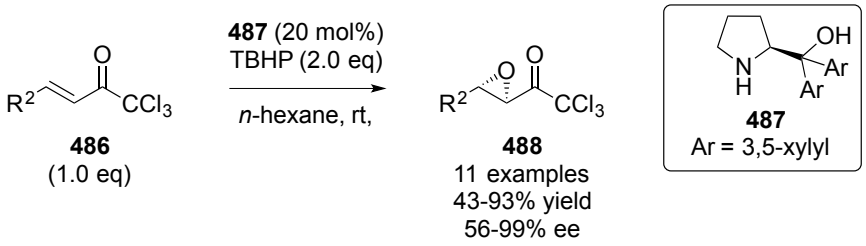
Scheme 88 - Application of acyl phosphonates as ester/amide surrogates in H-bonding catalysis.

Encouraged by the application of α,β-unsaturated phosphonates in organocatalysis, in 2014 the Smith group reported a Michael addition-lactonisation process using α,β-unsaturated ketophosphonates as ester/amide surrogates (Scheme 89). Reaction of arylacetic acids **482** with α-ketophosphonates **483** in the presence of *t*-BuCOCl, *i*-Pr_2NEt and catalyst (2*S*,3*R*)-HyperBTM **53** (10 mol%) provides phosphonate dihydropyranones **484** in moderate to good yield (49-83%) and excellent diastereo- and enantioselectivity (91:9->95:5 dr and 86-98% ee). Generally, this procedure was used in conjunction with an *in situ* ring opening and subsequent substitution of phosphate giving access to the corresponding chiral diesters and diamides **485** with maintenance of the high levels of enantiocontrol.



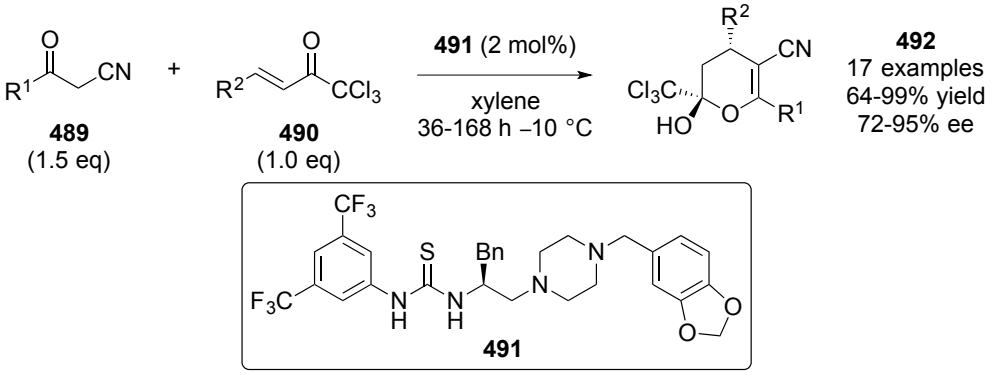
Scheme 89 - α-Ketophosphonates as ester/amide surrogates in asymmetric isothiourea-catalysis.

Despite the good results from this methodology, a significant limitation was the poor long term bench-stability of the α-ketophosphonates. To alleviate this limitation it was proposed that an α,β-unsaturated ester equivalent such as the trichloromethyl ketones may be more stable alternatives. Trichloromethyl ketones have proved to be useful synthetic building blocks with application as carboxylic acid, ester and amide surrogates, taking advantage of the leaving group ability of CCl_3 in haloform-type reactions.[112] Specifically, α,β-unsaturated trichloromethyl ketones have been utilised in enantioselective Michael additions in a small number of examples. In 2009, Zhao and co-workers reported the enantioselective epoxidation of α,β-unsaturated trichloromethyl ketones **486** with *tert*-butylhydroperoxide (TBHP) catalysed by prolinol derivative **487** (20 mol%) (Scheme 90).[113]



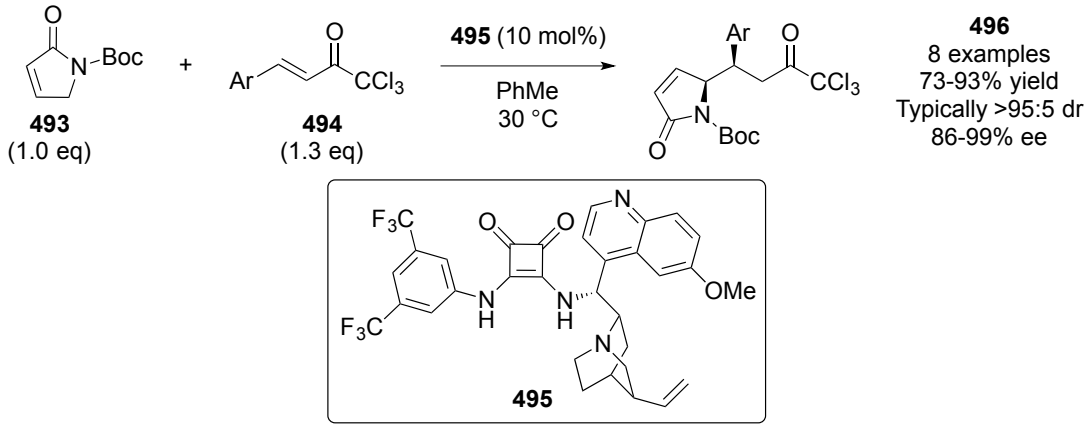
Scheme 90 - Application of α,β-unsaturated trichloromethyl ketones in enantioselective epoxidation.

Zhao and co-workers followed this work in 2011 with an enantioselective synthesis of α-trichlorodihydropyrans **492** in typically good to excellent yield (>84%) and enantioselectivity (72-95% ee) using trichloroketone **490** and α-cyano ketones **489** catalysed by piperazine/thiourea catalyst **491** (Scheme 91).



Scheme 91 - Application of α,β-unsaturated trichloromethyl ketones in enantioselective synthesis of α-trichlorodihydropyrans.

More recently, Wang and co-workers have applied α,β-unsaturated trichloromethyl ketones **494** in enantioselective vinylogous Michael additions with γ-butyrolactams **493** catalysed by squaramide **495** (10 mol%) to produce Michael adducts **496** in 73-93% yield, typically >95:5 dr and 86-99% ee (Scheme 92).



Scheme 92 - Application of α,β-unsaturated trichloromethyl ketones in enantioselective vinylogous Michael additions with γ-butyrolactams.

Inspired by the use of α,β-unsaturated trichloromethyl ketones as ester/amide surrogates in enantioselective Michael additions, it was hypothesised that these compounds may be suitable substrates for an isothiourea-catalysed Michael addition-lactonisation protocol (Figure 39). Furthermore, ring opening of the corresponding dihydropyranones and substitution of the CCl_3 group would provide stereodefined diesters or diamides. Overall, this process consists of a similar design to that conducted previously with α,β-unsaturated ketophosphonates but with bench-stable substrates that can be stored for long periods of time and a wider scope of examples available.

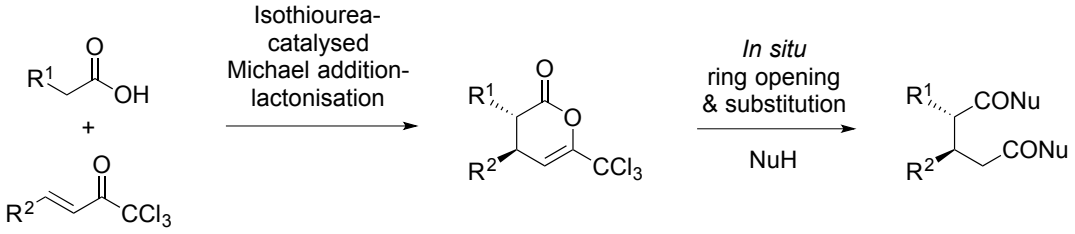


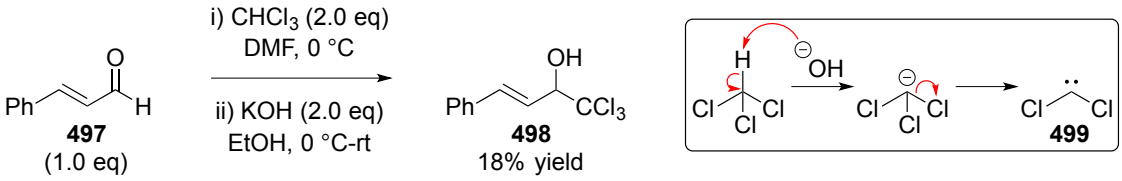
Figure 39 - Project design applying α,β-unsaturated trichloromethyl ketones in isothiourea-catalysed Michael addition-lactonisation/ring opening-substitution process

5.2 Michael Addition-Lactonisation Initial Results

5.2.1 Synthesis of α,β-Unsaturated Trichloromethyl Ketones

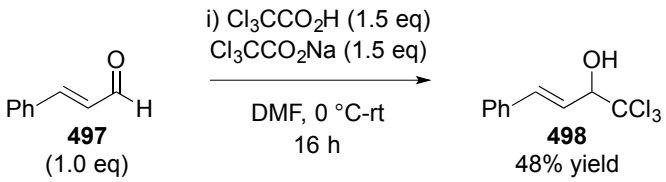
Despite the use of α,β-unsaturated trichloromethyl ketones in the chemical literature, the synthesis of these substrates is not trivial. Therefore, to make this methodology practical, a reliable synthesis of the α,β-unsaturated trichloromethyl ketones was necessary. The first attempted synthesis used the procedure described by Zhao and co-workers.[113] Treatment of a solution of cinnamaldehyde **497** and $CHCl_3$ in DMF at 0 °C with a solution of KOH in EtOH and stirring at 0 °C provided some unusual results (Scheme 93). Analysis of the crude reaction

by ^{1}H NMR spectroscopy appeared promising, with allylic alcohol **498** and starting material **497** observed as the only components in a 85:15 ratio (**498**:**497**). However, following column chromatography **498** was isolated in a disappointing 18% yield. To examine if allylic alcohol **498** was unstable to chromatography the product was stirred in a solution of silica gel and CH_2Cl_2. After 4 h, no decomposition of **498** was observed by ^{1}H NMR spectroscopy with the full mass returned, consistent with instability to silica gel not being responsible for the poor yield. Characteristic of these reaction mixtures was a dark black colour consistent with either decomposition or polymerisation. Typically the colour change from colourless to black occurred following the addition of KOH in EtOH. These reaction conditions have been commonly used in a number of transformations, such as the Reimer-Tiemann reaction,[114] to generate the highly reactive dichlorocarbene intermediate **499**. This can in turn lead to further side reactions and decomposition, with much of the polymeric material formed observable by ^{1}H NMR spectroscopy. This observation is consistent with the observed clean crude ^{1}H NMR but poor isolated yield.



Scheme 93 - Preparation of 498 using the procedure from Zhao and co-workers.

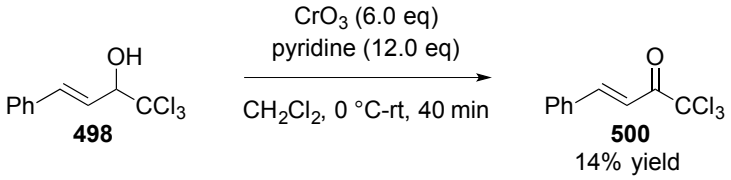
Next, an alternative synthesis of **498** following the procedure reported by Wang and co-workers was investigated.[115] Reaction of cinnamaldehyde **497** with trichloroacetic acid and sodium trichloroacetate in DMF for 2 h gave product **498** in poor 15% conversion (as determined by ^{1}H NMR spectroscopy). Heating the reaction to 50 °C led to complete decomposition of starting materials within 1 h. Pleasingly, conducting the reaction at 0 °C and slowly allowing the reaction to warm back to rt overnight provided **498** with full consumption of **497** and an isolated yield of 48% (Scheme 94).



Scheme 94 - Preparation of 498 using the procedure from Wang and co-workers.

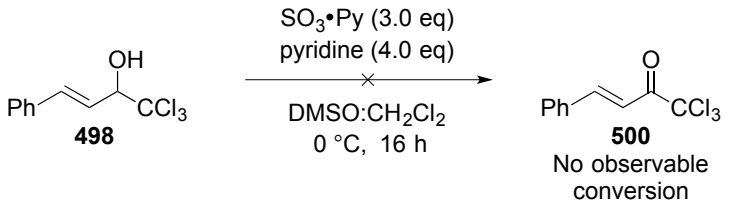
With allylic alcohol **498** in hand, the next step was the oxidation into the corresponding α,β-unsaturated trichloromethyl ketone **500**. The first reaction investigated was a Jones oxidation based on the procedure reported by Wang and co-workers (Scheme 95).[115] Addition of **498** to excess CrO_3 and pyridine at 0 °C gave a small conversion into ketone **500** with a

complex crude mixture of decomposition material obtained leading to isolation of **500** in only in 14% yield.



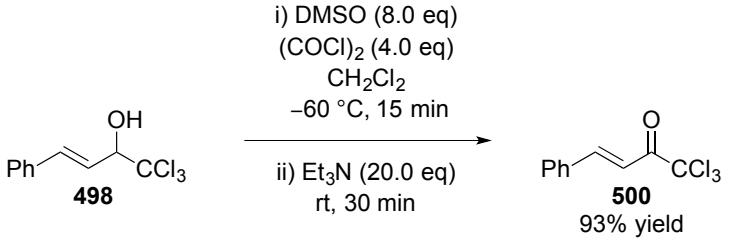
Scheme 95 - Attempted Jones oxidation of 498.

The next transformation tried was a Parikh-Doering oxidation using a modified protocol to that reported by Evans and co-workers (Scheme 96).[116] Treatment of allylic alcohol **498** with sulfur trioxide pyridine complex, pyridine and freshly distilled DMSO in CH_2Cl_2 gave no conversion into ketone **500** with only starting materials returned.



Scheme 96 - Attempted Parikh-Doering oxidation of 498.

Finally, the Swern oxidation procedure as demonstrated by Corey and co-workers proved successful (Scheme 97).[117] Reaction of **498** with DMSO and oxalyl chloride at −60 °C followed by addition of excess Et_3N gave trichloromethyl ketone **500** in excellent 93% yield.



Scheme 97 - Swern oxidation of 498.

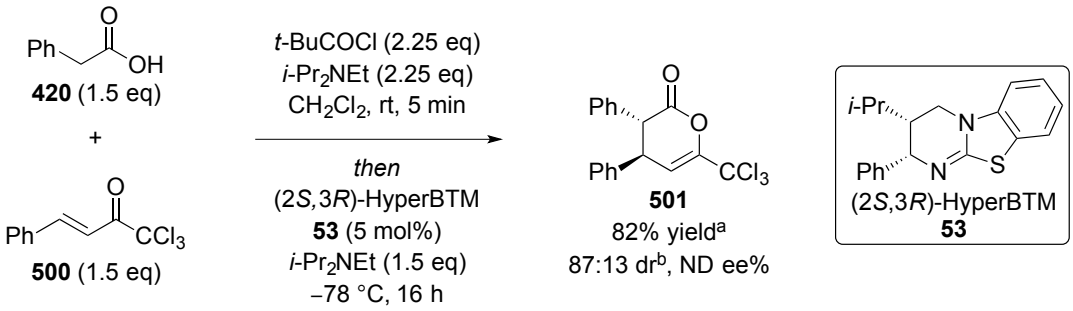
Following the establishment of a synthetic route to synthesise α,β-unsaturated trichloromethyl ketones, a range was prepared by colleagues within the Smith group.[118]

5.3 Michael addition-Lactonisation/Ring Opening Cascade

5.3.1 Initial Results

Based on the successful application of structurally related CF_3 enones and carboxylic acids in isothiourea-catalysed Michael addition-lacontisation processes the optimum conditions from these systems were applied to CCl_3 ketones.[42],[119] Reaction of phenylacetic acid **420** with pivaloyl chloride, *i*-Pr_2NEt and trichloromethyl ketone **500** in the presence of (2*S*,3*R*)-

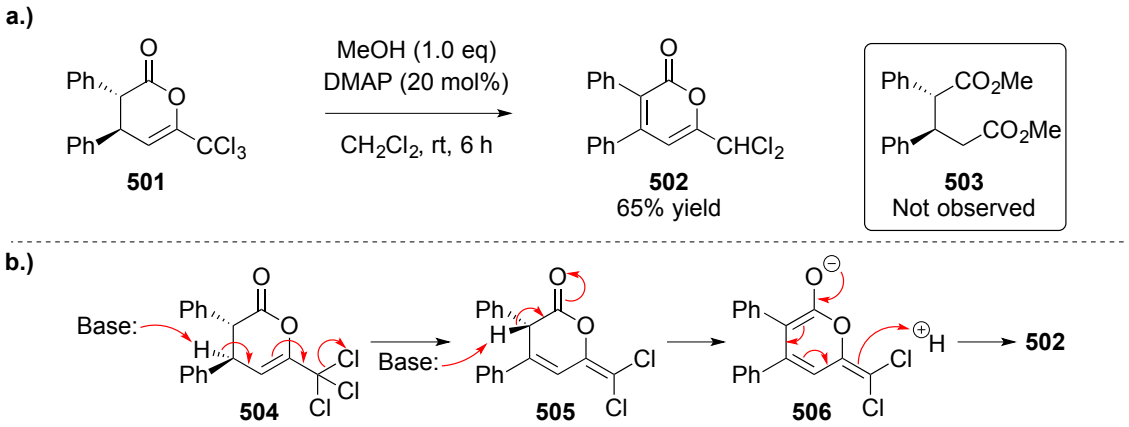
HyperBTM **53** (5 mol%) gave *anti*-dihydropyranone **501** in 82% yield and 87:13 dr (Scheme 98). Dihydropyranone **501** was unstable to storage and underwent with decomposition within a week even when kept below 0 °C. Moreover the lack of stability led to decomposition of **501** when subject to either chiral HPLC or GC, making determination of the reaction enantioselectivity unsuccessful.



[a]Isolated by column chromatography as 87:13 dr. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture.

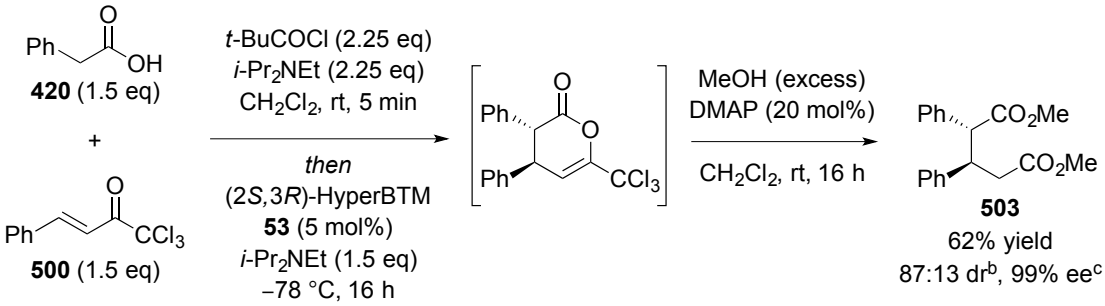
Scheme 98 - Application of α,β-unsaturated trichloromethyl ketone 500 in Michael addition-lactonisation.

It was proposed that transformation of **501** into the corresponding diester *via* an *in situ* ring opening and substitution of the CCl_3 ketone would provide products with improved stability. Dihydropyranone **501** was reacted with one equivalent of MeOH and substoichiometric DMAP at rt for 6 h giving full consumption of **501** (Scheme 99). The ^{1}H NMR analysis of the crude mixture did not indicate the formation of the intended diester **503**, however. Following purification by column chromatography the reaction product was determined to be pyrone **502**. A possible mechanism for the formation of **502** is deprotonation at C(4) and elimination of Cl^- to give **505**. Formal tautomerisation of **505** leads to dichloromethyl pyrone **502**.



Scheme 99 - a.) Attempted ring opening of 501 with 1.0 eq MeOH and 20 mol% DMAP. b.) Proposed mechanism for the formation of 502.

An alternative protocol with an *in situ* ring opening using a large excess of MeOH was examined and pleasingly produced diester **503** in 62% yield, 87:13 dr and 99% ee with no observation of pyrone **502** (Scheme 100).

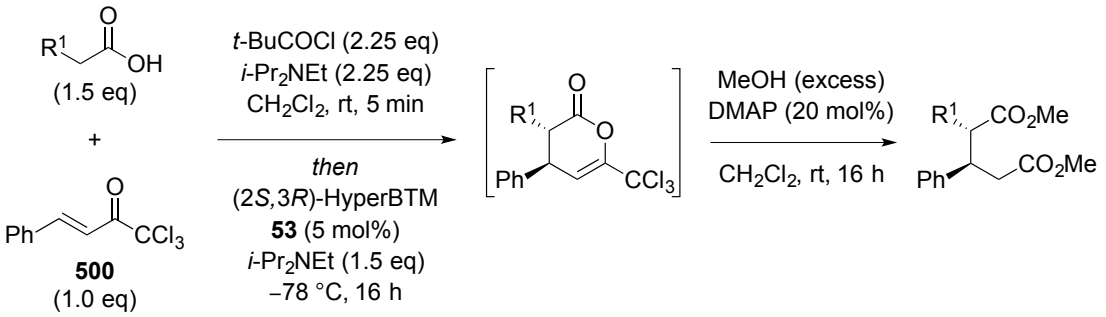


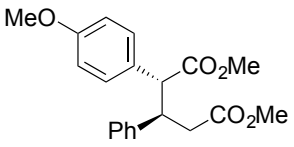
[a]Isolated by column chromatography. [b]Determined by ^{1}H NMR spectroscopy (isolated as >95:5 dr). [c]Determined by chiral HPLC analysis.

Scheme 100 - Michael addition-lactonisation/*in situ* ring opening protocol.

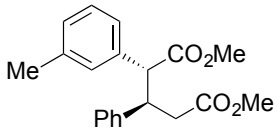
5.3.2 Substrate scope

With a suitable Michael addition-lactonisation/*in situ* ring opening protocol established, the reaction scope was next evaluated. Firstly, a selection of acetic acids was tested with trichloromethyl ketone **500** (Table 26). Electron-rich carboxylic acids worked well with the 4-$MeOC_6H_4$ substituent incorporated in **507** with 77% yield, 92:8 dr and >99% ee. The 3-MeC_6H_4 substituted acetic acid was tolerated providing **508** in 65% yield, 85:15 dr and 91% ee. Unfortunately, the 2-MeC_6H_4 variant **509** gave poor conversion, most likely due to the steric demand of the 2-substituted aromatic substituent. Thienyl example **510** was prepared in good 64% yield, 81:19 dr and >99% ee. Expanding the scope beyond only arylacetic acids, the propenyl and phenylpropenyl products **511** and **512** proved successful with 78% and 74% yield, 85:15 and 95:5 dr and both >99% ee, respectively. Diesters **513-514** were produced by colleagues within the Smith group.[120] The scope could not be extended to alkyl-substituted acetic acids with 3-phenylpropanoic acid giving no conversion into product **515**.

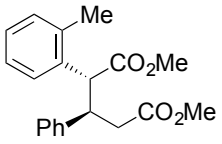




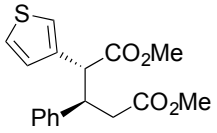
507
77% yield[a]
87:13 dr[b], 99% ee[c]



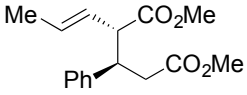
508
60% yield[a]
92:8 dr[b], 99% ee[c]



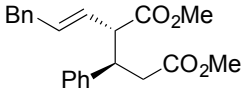
509
<10% conversion[b]



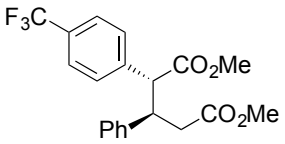
510
64% yield[a]
81:19 dr[b], >99% ee[c]



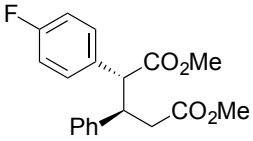
511
78% yield[a]
85:15 dr[b], >99% ee[c]



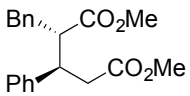
512
74% yield[a]
95:5 dr[b], >99% ee[c]



513
65% yield[a]
85:15 dr[b], 91% ee[c]



514
69% yield[a]
90:10 dr[b], 99% ee[c]

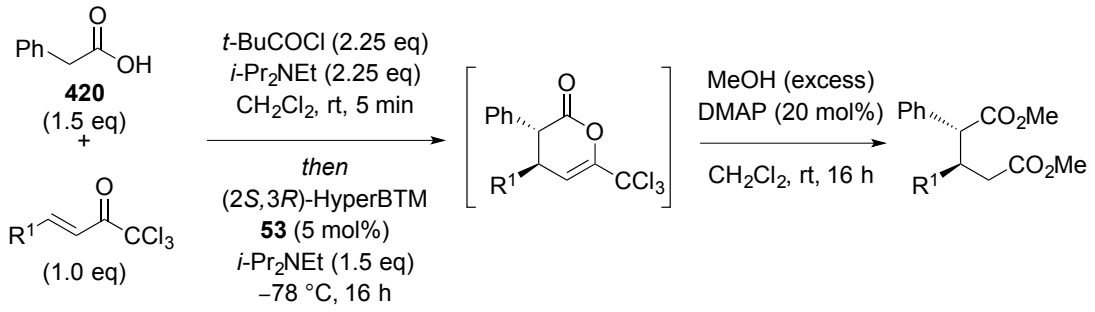


515
<5% conversion[b]

[a]Isolated by column chromatography as >95:5 dr. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by chiral HPLC analysis.

Table 26 - Substrate scope: variation of carboxylic acid.

A number of different trichloromethyl ketone Michael acceptors was subjected to the previously optimised conditions applying phenyl acetic acid **420**. The diester products **516-519** with varying groups at the C(3) positions were prepared by colleagues within the Smith group (Table 27). [121]



516
73% yield[a]
90:10 dr[b], >99% ee[c]

517
80% yield[a]
95:5 dr[b], >99% ee[c]

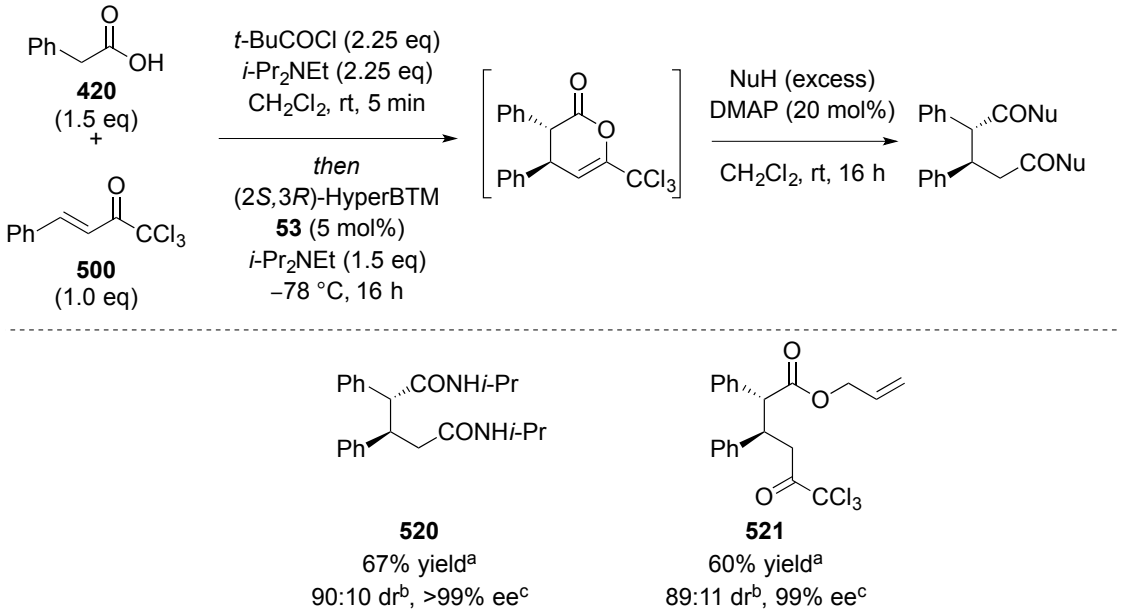
518
70% yield[a]
87:13 dr[b], 99% ee[c]

519
80% yield[d]
80:20 dr[b], 98% ee[c] (*anti*)
23% ee[c] (*syn*)

[a]Isolated by column chromatography as >95:5 dr. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by chiral HPLC analysis. [d]Isolated as mixture of diastereoisomers (80:20 dr)

Table 27 - Substrate scope: variation in Michael acceptor conducted by colleagues within the Smith group.

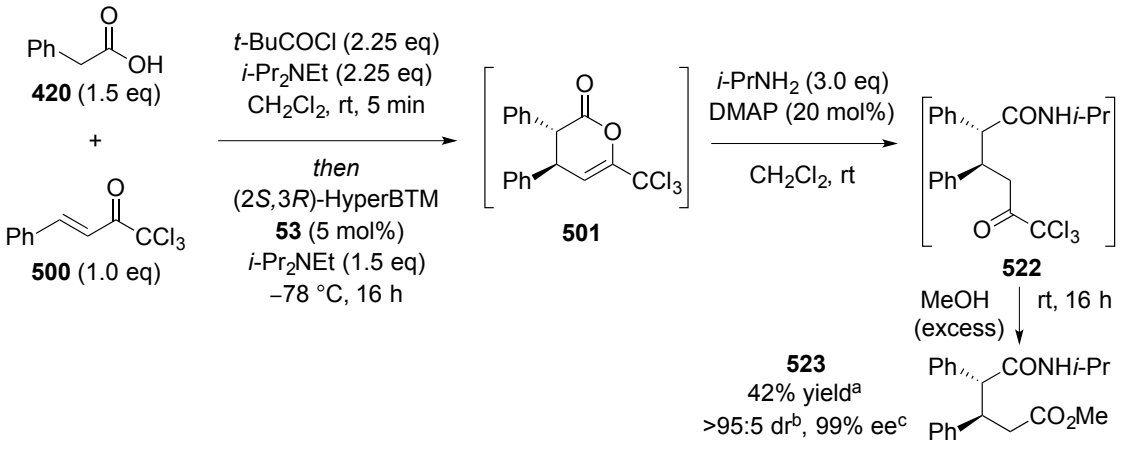
Lastly, different nucleophiles were investigated for the ring opening-CCl_3 substitution by the Smith group with some interesting results (Table 28). Amines can be used to give stereodefined diamide **520** in 67% yield, 90:10 dr and >99% ee. Using allyl alcohol in the procedure successfully opens the dihydropyranone, but does not substitute the CCl_3 group giving trichloromethyl keto ester **521** in 60% yield and comparable stereoselectivity.



[a]Isolated by column chromatography as >95:5 dr. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by chiral HPLC analysis.

Table 28 - Substrate scope: alternative nucleophiles.

Overall, it was observed in all examples that ring opening of the dihydropyranone with the requisite nucleophile is relatively quick (typically under 4 h) whereas substitution of the CCl_3 proceeds much slower (typically 12 h). To take advantage of this characteristic, the intermediate ring opened trichloromethyl keto-amide **522** was intercepted with addition of excess MeOH to give γ-ester amide **423** in moderate 42% yield but with excellent >95:5 dr and 99% ee (Scheme 101).[122]



[a]Isolated by column chromatography as >95:5 dr. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by chiral HPLC analysis.

Scheme 101 - Sequential ring opening with different nucleophiles.

5.4 Proposed Mechanism

The proposed mechanism for this process starts *via N*-acylation of (2*S*,3*R*)-HyperBTM **53** with *in situ* formed mixed anhydride **524** forming acyl ammonium **525** (Figure 40). Deprotonation of **525** gives the key (*Z*)-ammonium enolate **526**, allowing either an n_o to $\sigma^*_{C\text{–}S}$ interaction or favourable electrostatic stabilisation between the enolate oxygen and the sulfur atom of the isothiourea.[36-37, 101b] Enantioselective Michael addition to α,β-unsaturated trichloromethyl ketone **527** followed by lactonisation gives dihydropyranone **529** and regenerates the catalyst. Ring opening of dihydropyranone **529** with a nucleophile and further substitution of the trichloromethyl ketone gives **530**.

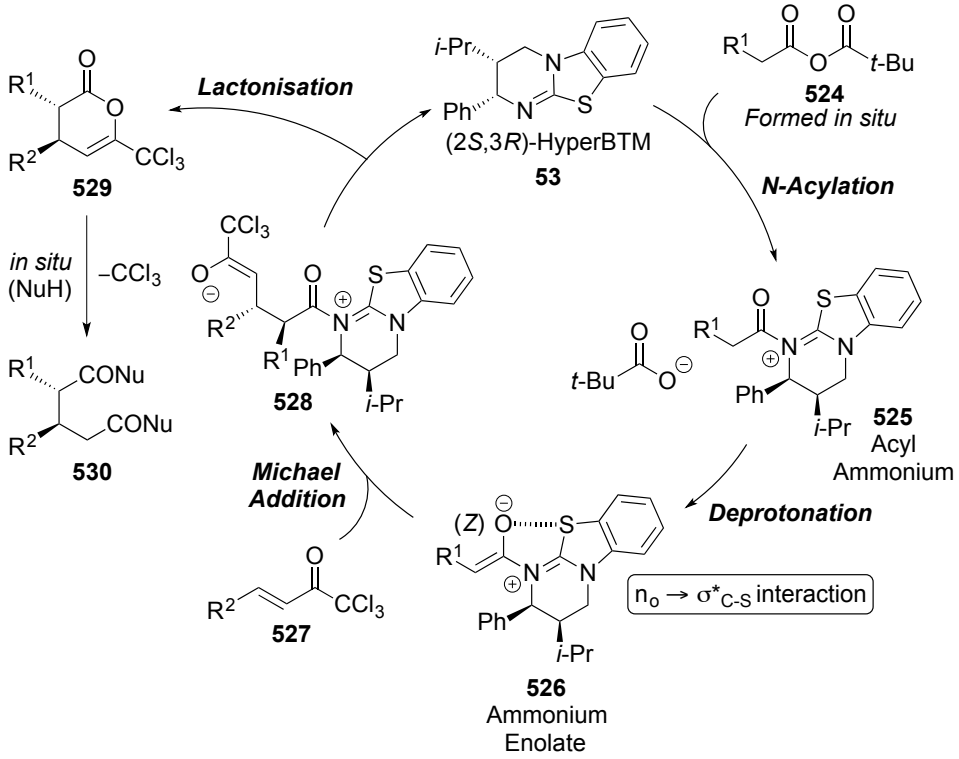


Figure 40 - Proposed reaction mechanism.

5.5 Conclusions

In conclusion, a practical and reproducible synthesis of α,β-unsaturated trichloromethyl ketones has been developed. Application of these α,β-unsaturated trichloromethyl ketones in an isothiourea-catalysed Michael addition-lactonisation protocol provides *anti*-dihydropyranones that are ring opened *in situ* with addition of a nucleophile and subsequent substitution of CCl_3 group produces access to a range of stereodefined chiral diesters in typically excellent enantioselectivity. Further investigation within the Smith has discovered a sequential ring opening-CCl_3 substitution with two different nucleophiles.

5.6 References and Notes

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[119] Full reaction optimisation carried out by James Squires, MChem 5th Year Project "Asymmetric Isothiourea-Mediated Organocatalytic Formation of Di-Esters *via* Ammonium Enolates".

[120] Synthesis of examples **514**-**516** carried out by L. C. Morrill (PhD student, Smith Group) and Dr J. E. Taylor (PDRA, Smith Group). Full details included in ref 103.

[121] Synthesis of examples **517**-**520** carried out by L. C. Morrill (PhD student, Smith Group) and Dr J. E. Taylor (PDRA, Smith Group). Full details included in ref 103.

[122] Synthesis of examples **523** carried out by Dr J. E. Taylor (PDRA, Smith Group). Full details included in ref 103.

Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 6: Isothiourea-Catalysed Enantioselective Synthesis of Pyrrolizines

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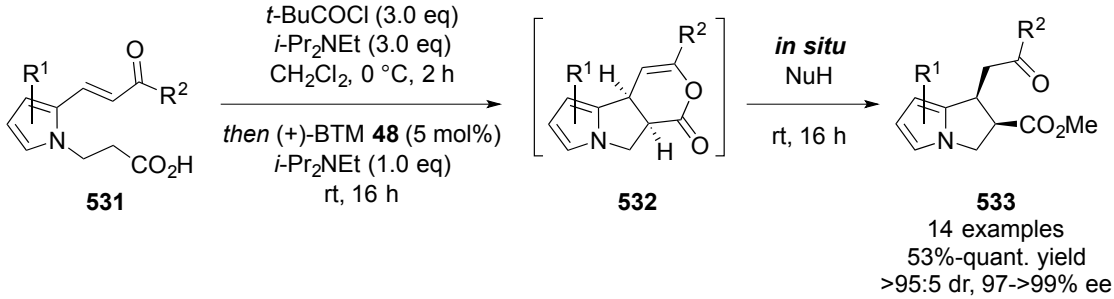
Chapter 6: Isothiourea-Catalysed Enantioselective Synthesis of Pyrrolizines

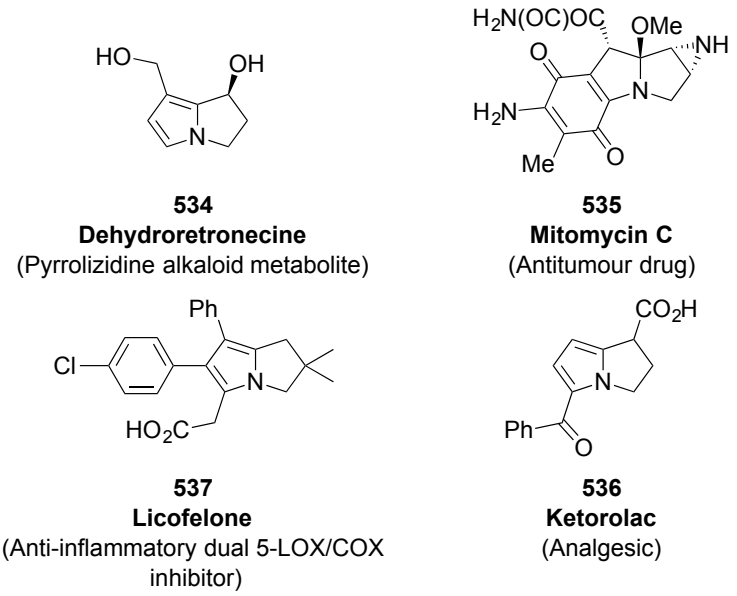
This chapter describes an enantioselective synthesis of pyrrolizines *via* an isothiourea-catalysed Michael addition-lactonisation process. An efficient and reproducible route to prepare a range of pyrrolo enone-acid substrates has been established. Application of pyrrolo enone-acids in a (+)-BTM **48** (5 mol%) catalysed Michael addition-lactonisation gives dihydropyranone pyrrolizines **532** *in situ*. A range of nucleophiles have been used to undergo ring opening of **532** to provide pyrrolizines **533** in typically excellent yield (53%-quant. yield), diastereo- and enantioselectivity (>95:5 dr and 97-99% ee) (Scheme 102).



Scheme 102 - Enantioselective isothiourea-catalysed synthesis of pyrrolizines.

6.1 Introduction

The 5,5-bicyclic pyrrolizine and pyrrolizidine structural motifs are present at the core of many biologically active natural products,[123] such as that of dehydroretronecine **534** (Figure 41).[124] This natural product, along with many other derivatives, originates from metabolism of the pyrrolizidine alkaloids (PA's), a natural alkaloid prevalent in plant life throughout nature.[125] Such PA derived molecules are known to be potent heptatoxins,[126] carcinogens,[127] teratogens[128] and genotoxins.[129] Compelled by such levels of biological activity, it is no surprise that many of these natural products have become commercial therapeutic agents with many more synthetic derivatives now also being developed. An early and classic example is that of partially reduced pyrrolizine mitomycin C **535**, isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae* this chemotherapeutic agent has been found to be a potent antitumour antibiotic drug with a broad scope of applications.[130] The non-steroidal anti-inflammatory drug (NSAID), Licofelone **536** has shown great promise in osteoarthritis treatment through a dual inhibition of 5-LOX/COX.[131] Additionally, another pyrrolizine based NSAID, Ketorolac **537**, has found success as a commercial analgesic.[132]



534
Dehydroretronecine
(Pyrrolizidine alkaloid metabolite)

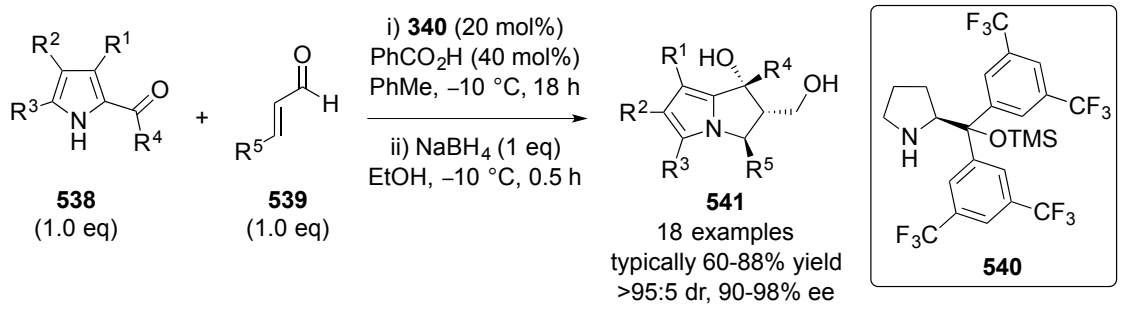
535
Mitomycin C
(Antitumour drug)

537
Licofelone
(Anti-inflammatory dual 5-LOX/COX inhibitor)

536
Ketorolac
(Analgesic)

Figure 41 - Biologically relevant pyrrolizines.

Despite the value and potential of these bicyclic compounds, methodologies that enable efficient access to diverse structural libraries are limited. Many syntheses have involved classic total synthesis approaches towards specific target molecules.[133] One of the first catalytic methods was reported by Cho and co-workers in 2010 with an enantioselective organocatalysed Michael addition-aldol reaction (Scheme 103).[134] Reaction of proline derivative **540** (20 mol%) with pyrroles **538** and enals **539** in the presence of benzoic acid allows the initial Michael addition-aldol reaction to form the bicyclic motif with reduction by $NaBH_4$ providing the pyrrolizine alcohols **541** in excellent yield and stereoselectivity (>95:5 dr and 90-98% ee).



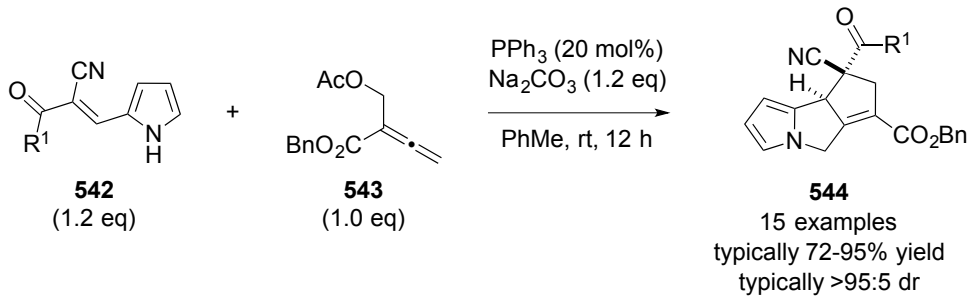
538
(1.0 eq)

539
(1.0 eq)

541
18 examples
typically 60-88% yield
>95:5 dr, 90-98% ee

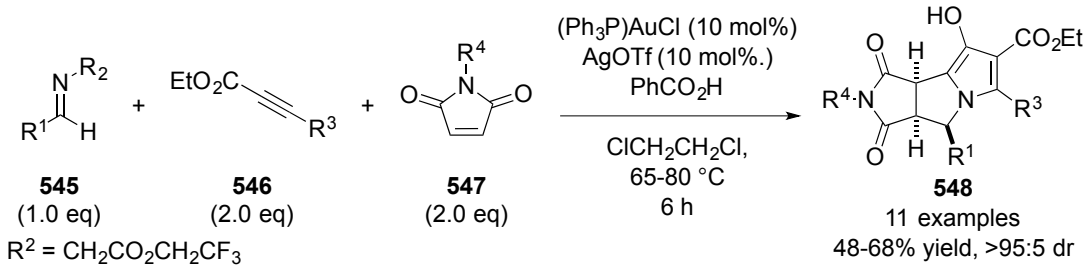
Scheme 103 - Pyrrolizine synthesis via organocatalysed Michael addition-Aldol reaction.

In recent years the state-of-the-art in pyrrolizine synthesis has involved multi-component domino reactions with one example being the phosphine-catalysed protocol by Tong and co-workers (Scheme 104).[135] Reaction of pyrrolo enones **542**, allenes **543**, Na_2CO_3 and catalysed by PPh_3 (20 mol%) gives tricyclic pyrrolizines in a proposed concerted cycloaddition process. This process produces the desired products in **544** in excellent yield (72-95%) and diastereoselectivity (>95:5 dr) but in racemic form.



Scheme 104 - PPh_3-catalysed diastereoselective synthesis of pyrrolizines.

A further example was reported recently but Matsuya and co-workers with a gold-catalysed three-component domino process (Scheme 105).[136] Treatment of aldimines **545**, maleimides **547** and alkynes **546** with catalyst $(Ph_3P)AuCl$ (10 mol%) gives pyrrolizine products **548** in moderate to good yield (48-68%) and excellent diastereoselectivity (>95:5 dr). As with the previous example, this procedure does not offer an enantioselective option and therefore is limited to the synthesis of racemic mixtures.



Scheme 105 - Gold-catalysed diastereoselective domino synthesis of pyrrolizines.

6.2 Previous Work

In spite of the new advances in this area there is still a requirement for easily accessible, catalytic methodologies that can produce the chiral pyrrolizine derivatives with high enantiocontrol. As already introduced in Chapter 1, the Smith group has previously reported methods to synthesise fused-polycyclic compounds *via* enantioselective-catalysis.[41] Specifically, following the intramolecular isothiourea-catalysed synthesis of indanes, benzofurans and tetrahydrofurans, it was proposed that this methodology may provide a plausible route into chiral pyrrolizines **549** using pyrrolo enone-acids **550** as substrates (Figure 42).

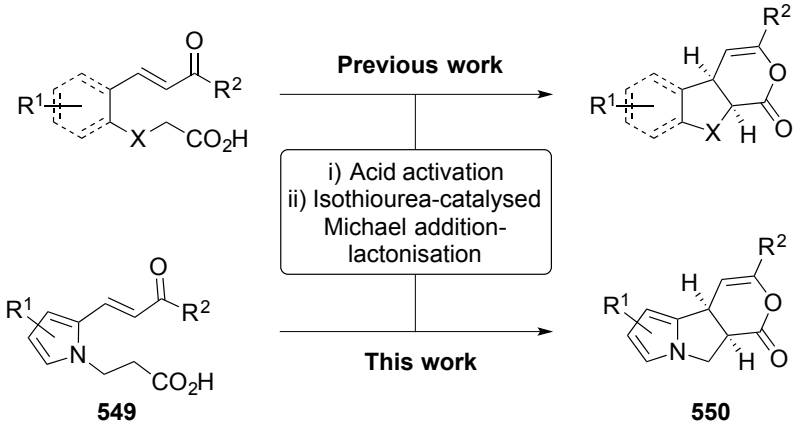


Figure 42 - Proposed enantioselective synthesis of pyrrolizines.

Initial studies within the Smith group started the project with an investigation into the synthesis of the required pyrrolo enone-acid substrates (Figure 43).[137] Firstly, pyrrole 2-carboxaldehydes **552** were purchased or prepared using a Vilsmeier-Haack formylation before *N*-alkylation with with 3-methylbromopropanoate to give **553**. Subsequent ester hydrolysis to acid **554** followed by Horner-Wadsworth-Emmons reaction gives pyrrolo enone-acids **555**. Although this process provided the parent phenyl containing substrate in good yield, the route proved problematic with alternative substrates not accessible and isolated yields not reproducible.

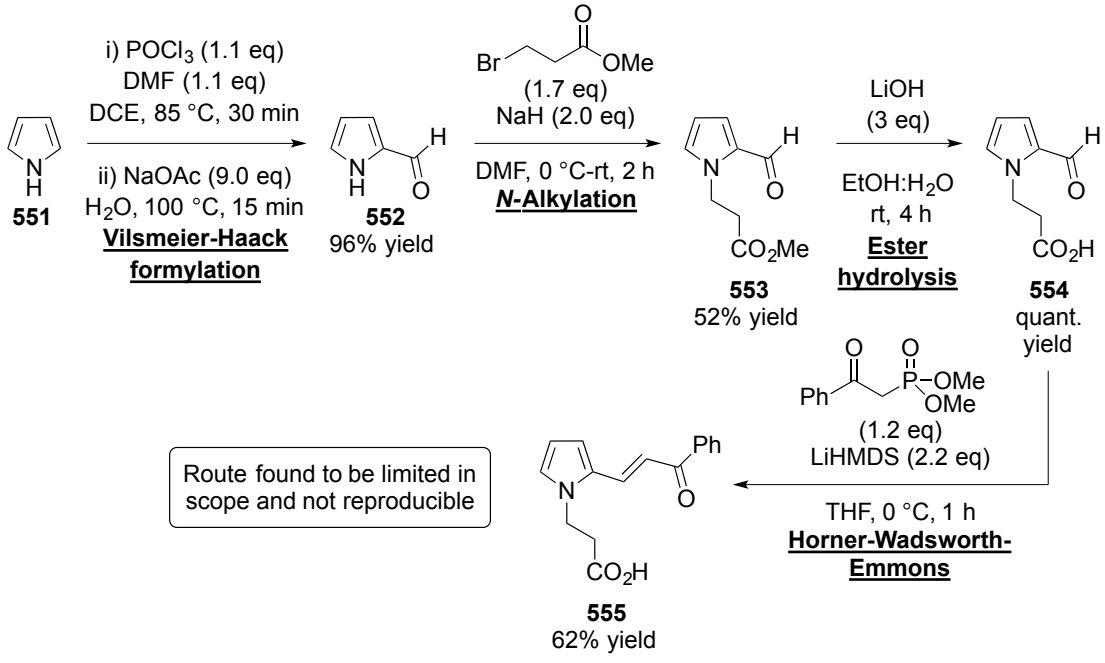
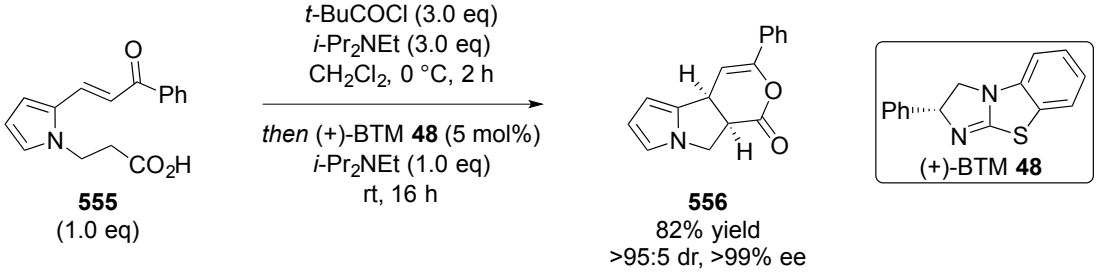


Figure 43 - Initial synthetic strategy for the synthesis of pyrrolo enone-acids attempted by colleagues within the Smith group.

The synthesis of pyrrolo enone-acid **555** allowed for the optimisation of an isothiourea-catalysed Michael addition-lactonisation process. It was discovered that treatment of the pyrrolo

enone-acid **555** for 2 h with pivaloyl chloride and *i*-Pr_2NEt followed by addition of (+)-BTM **48** (5 mol%) and further stirring at rt for 16 h provided *syn*-pyrrolizine dihydropyranone **556** in 82% yield, >95:5 dr and >99% ee (Scheme 106).

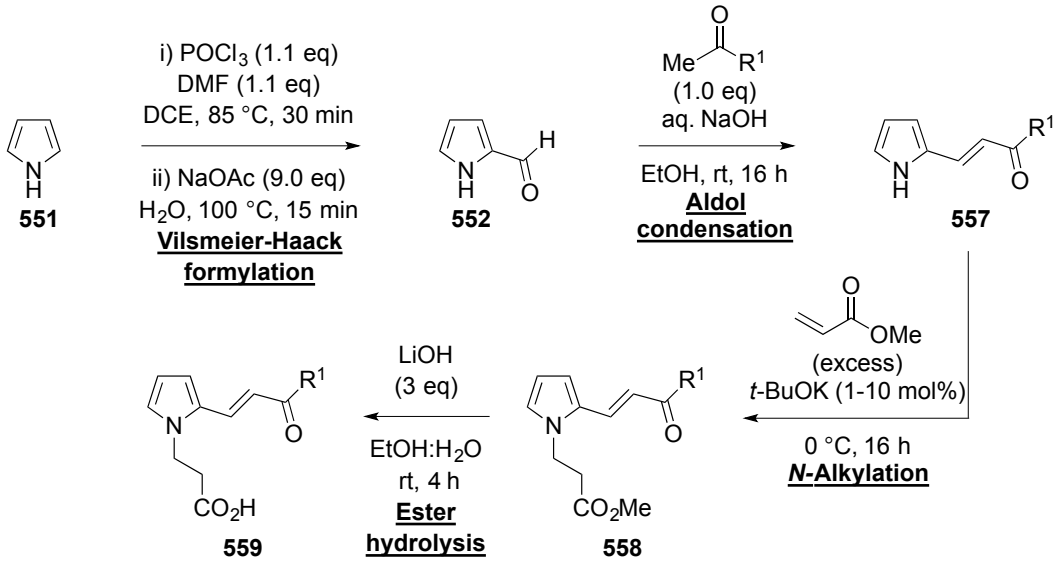


Scheme 106 - Optimised Michael addition-lactonisation procedure.

6.3 Synthesis of Pyrrolo Enone-Acid Substrates

6.3.1 Optimisation of a Synthetic Route

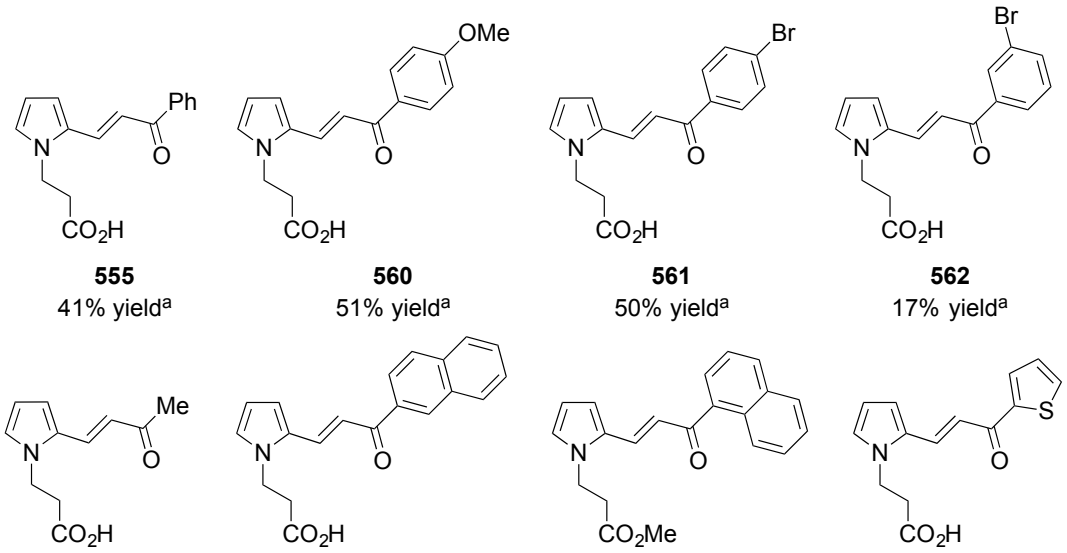
At the onset of the project, with the catalysis optimised, the first objective was to establish a general, reproducible synthetic route towards the required pyrrolo enone-acid substrates. Pleasingly, a modified strategy was devised that circumvents the problems with the first attempted synthetic route (Scheme 107). Pyrrole 2-carboxaldehydes **552** are treated with the requisite ketones and NaOH in an aldol condensation to give pyrrolo enones **557**. Subsequent *N*-alkylation was achieved using methyl acrylate and substoichiometric *t*-BuOK to produce pyrrolo enone-esters **558**. Finally, ester hydrolysis gives pyrrolo enone-acids **559**. In most cases, these steps do not require column chromatography with products provided in good purity or purified by recrystallisation or acid-base extraction techniques. Furthermore, it was found that this synthetic process was efficient, practical and provided a range of variants in good overall yield.



Scheme 107 - Optimised synthetic route towards pyrrolo enone-acids.

6.3.2 Preparation of Pyrrolo Enone-Acids

Using this synthetic route, a range of substrates **555, 560-566** were synthesised with differing substituents present on the enone component using the optimised procedure described previously (Table 29).

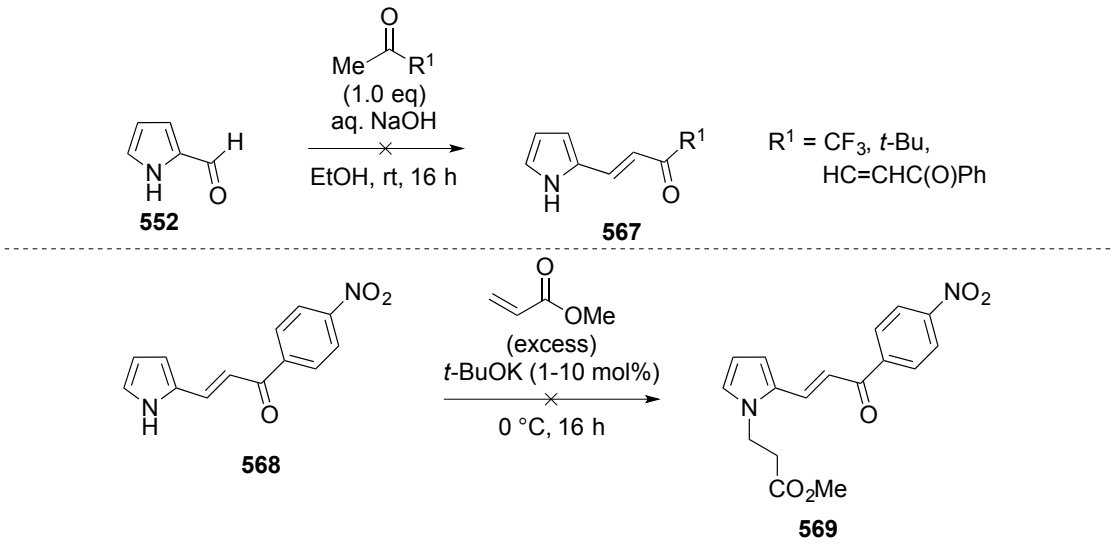


555	**560**	**561**	**562**
41% yield[a]	51% yield[a]	50% yield[a]	17% yield[a]
563	**564**	**565**[b]	**566**
58% yield[a]	27% yield[a]		20% yield[a]

[a]Yield over 3-steps. [b]Final product obtained as a crude mixture of 70-80% purity as determined by ^{1}H NMR spectroscopy.

Table 29 - Prepared pyrrolo enone-acids

Attempts to prepare further functionality within the enone proved difficult to obtain. Trifluoroacetone, 3,3-dimethylbutan-2-one and (*E*)-4-phenylbut-3-en-2-one gave no conversion in the aldol condensation with only starting materials returned (Scheme 108). Nitro containing pyrrolo enone **568** was synthesised however, when subject to the *N*-alkylation step this gave no conversion to product. It can be suggested that the strongly electron-withdrawing nitro substituent decreases the nucleophilicity of the pyrrole nitrogen and disfavours alkylation.



Scheme 108 - Unsuccessful examples.

To further explore the scope of the methodology it was necessary to prepare pyrrolo enone-acids that contain a substituted pyrrole backbone. The preliminary attempts, conducted by colleagues within the Smith group, focused on the synthesis of indolyl enone-acids with the added benzannulation of the parent pyrrolo enone-acid (Figure 44).[138] The success of the synthetic route used for the synthesis of pyrrolo enone-acids, disappointingly, did not transfer to the synthesis of indolyl enone-acids. With only small quantities of material accessible and a longer, more arduous synthesis that did not prove general or reproducible, this was not pursued any further. Additionally, the preparation of brominated pyrroles did not prove trivial with brominated pyrroles, in all cases, showing poor stability to light and heat and thus made isolation difficult.[139]

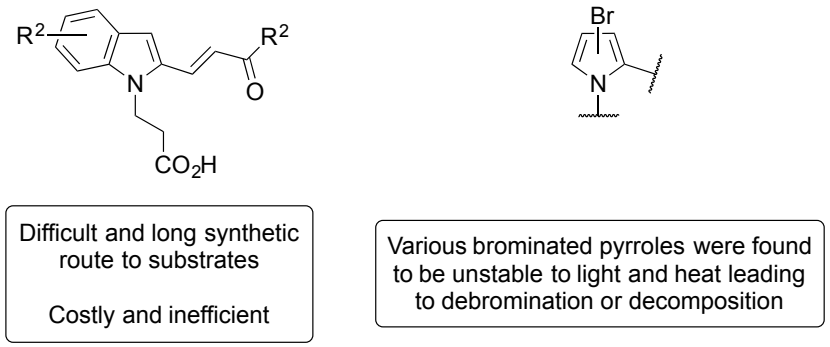
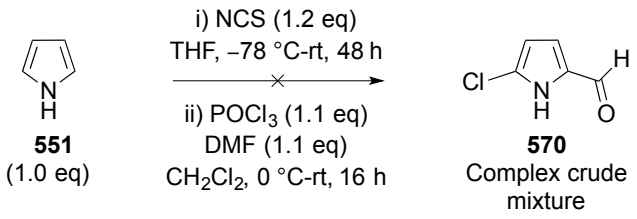


Figure 44 - Attempts at the synthesis of indolyl-based and brominated substrates by colleagues within the Smith group.

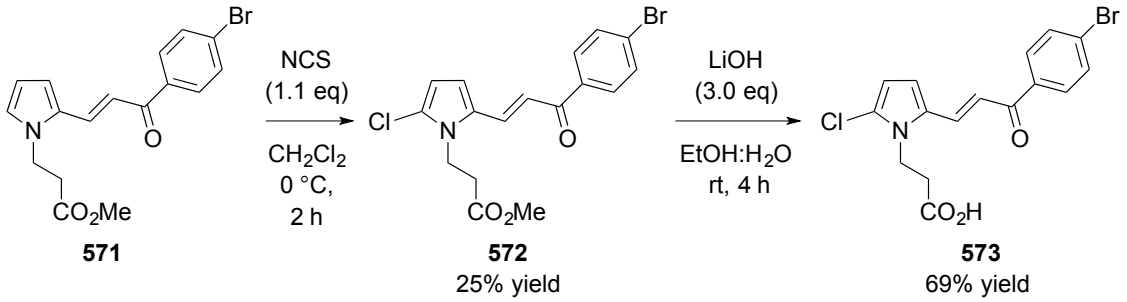
Chlorinated pyrrolo substrates were next assessed as it was hoped these would offer improved stability. A synthetic route towards a 5-chloro substituted substrate began with an attempted one-pot chlorination/formylation procedure from Reynolds and co-workers (Scheme 109).[140] This reaction gave a complex crude reaction mixture that appeared to be the result of

decomposition and polymerisation (determined by ^{1}H NMR spectroscopy), as is common with pyrrole-containing compounds.



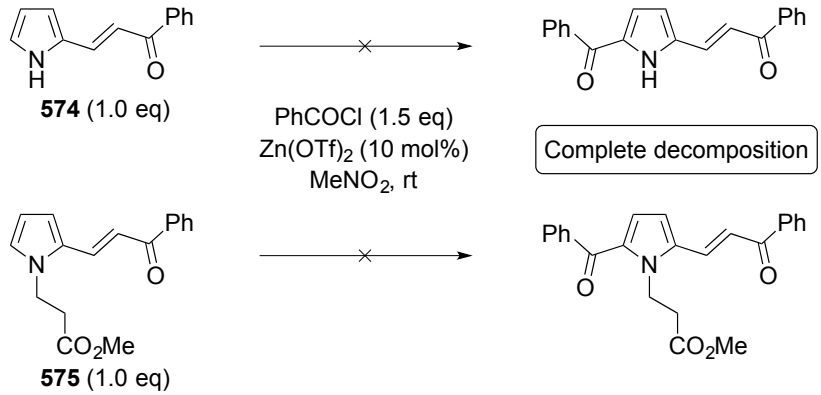
Scheme 109 - Attempted synthesis of 5-chloro pyrrole 2-carboxaldehyde.

Late stage chlorination was next evaluated, with treatment of pyrrolo enone-ester **571** with *N*-chlorosuccinimide (NCS) providing product **572** in 25% yield with subsequent hydrolysis giving the desired substrate **573** in 69% yield (Scheme 110).



Scheme 110 - Preparation of chloro pyrrolo enone-acid 573.

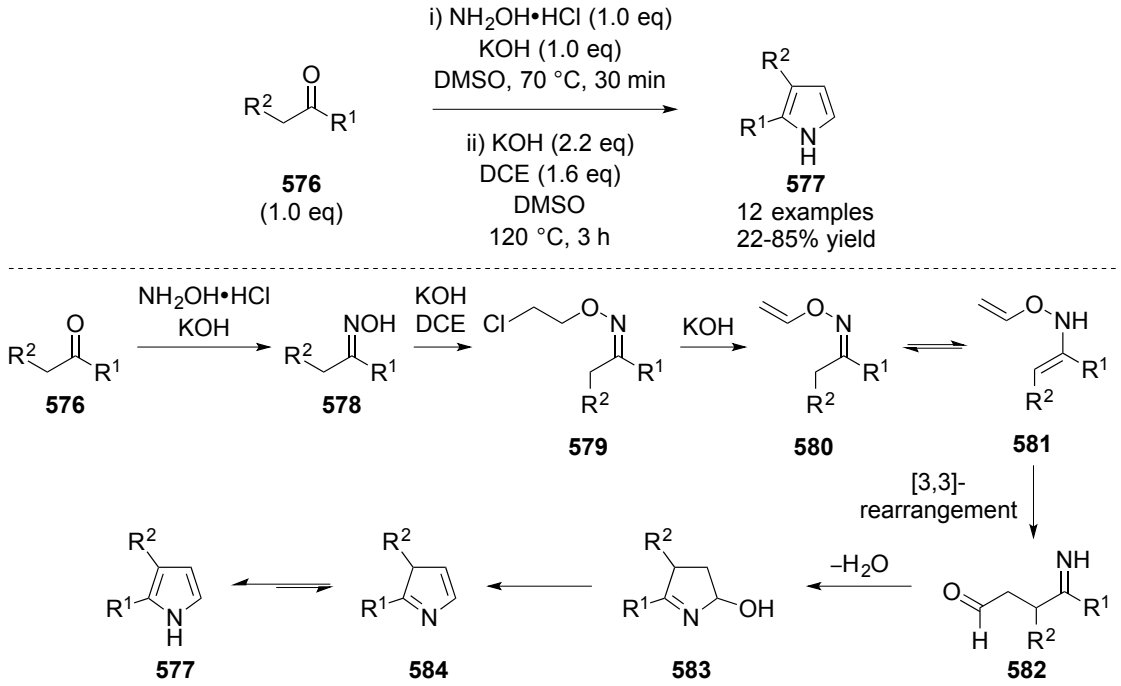
An alternative pyrrole functionalisation *via* Friedel-Crafts acylation, based on the procedure from Su and co-workers, using benzoyl chloride and $Zn(OTf)_2$ (10 mol%) was investigated on both pyrrolo enone **574** and pyrrolo enone-ester **575** (Scheme 111).[141] In both cases, complete decomposition was observed upon addition of $Zn(OTf)_2$ with a dark black residue obtained and no pyrrolic signals present in the ^{1}H NMR analysis of the crude mixture.



Scheme 111 - Attempted Friedel-Crafts acylation of 574 and 575.

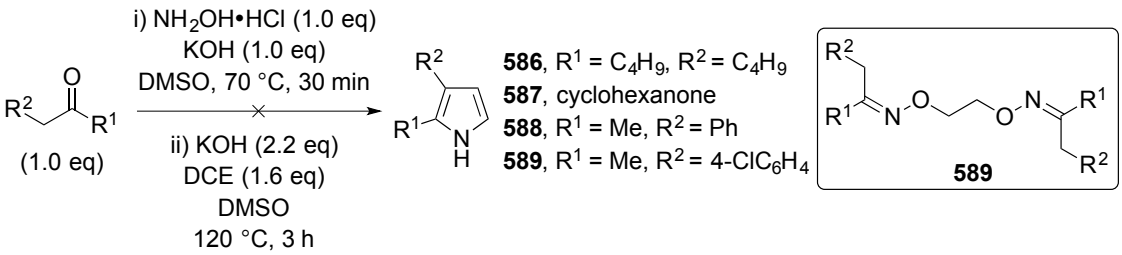
Following the report from Trofimov and co-workers in 2015 on the one-pot synthesis of pyrroles, it was suggested that this procedure would allow the preparation of a range of substituted pyrroles that could then be subjected to the optimised synthetic route mentioned

previously (Scheme 112).[142] Reaction of ketones **576** with NH_2OH•HCl, KOH and DCE gives substituted pyrroles **577** in typically moderate yields (11-85%). Following condensation of ketones **576** with NH_2OH•HCl in the presence of KOH it is proposed that oxime **578** forms, with deprotonation and alkylation on oxygen by DCE giving intermediate **579**. Subsequent elimination gives alkene **580** that upon heating to 120 °C promotes a [3,3]-rearrangement to give **582** that can then cyclise and aromatise to give pyrroles **577**.



Scheme 112 - Synthesis of substituted pyrroles by Trofimov and co-workers.

However, in our hands, this reaction proved largely unsuccessful. Reaction of a number of ketones did not provide any evidence for the formation of the pyrrole products with most reactions giving side-product **589** (Scheme 113).



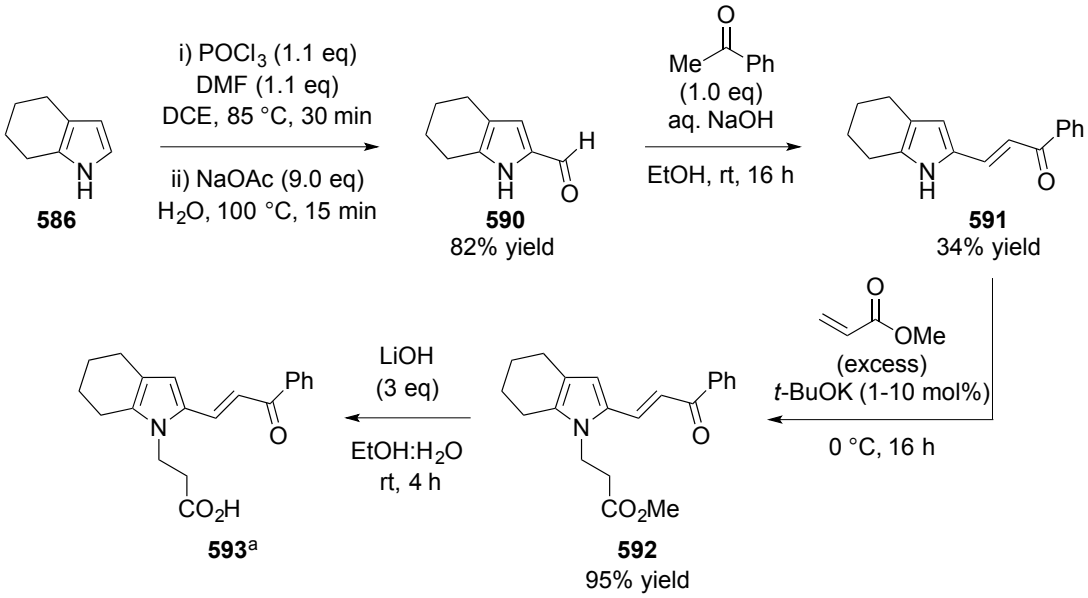
Scheme 113 - Attempted one-pot synthesis of substituted pyrroles.

A number of modifications were tried to obtain conversion into the required pyrroles. Conducting the reaction in a sealed-tube was tried as it was postulated that evaporation of DCE (or acetylene resulting from double elimination of DCE) was an issue but this did not offer any improvements. The equivalents of DCE were increased to five in order to fully alkylate all of the formed oxime and hence reduce the chance of generating side-product **589**. When applying

cyclohexanone a 13% yield of pyrrole **586** was achieved (Scheme 114). Attempts to apply other ketones remained unsuccessful when using this modified procedure.

Scheme 114 - Synthesis of tetrahydro-1*H*-indole 586.

With **586** in hand, it was submitted to the optimised synthesis to give enone-acid **593** (Scheme 115). This proved generally successful however, enone-acid **593** could not be fully purified and was obtained at 80% purity (as determined by ^{1}H NMR spectroscopy).



[a]Obtained as a crude mixture of 80% purity (as determined by ^{1}H NMR).

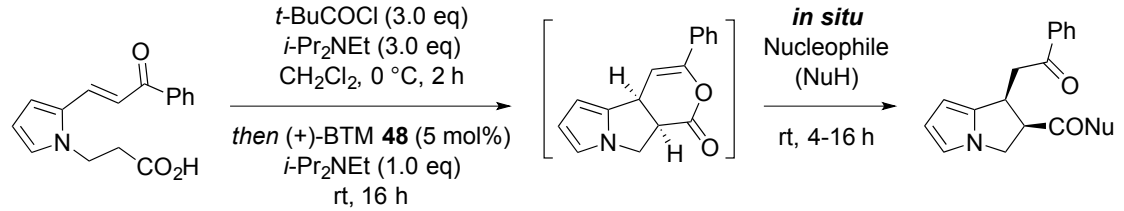
Scheme 115 - Synthesis of tetrahydro indolyl enone-acid 593.

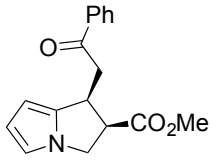
6.4 Substrate Scope

6.4.1 Michael Addition-Lactonisation/Ring Opening Scope: Variation of Nucleophile

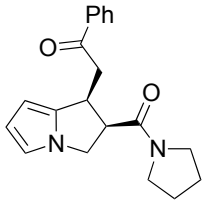
Disappointingly, when assessing the substrate scope, all pyrrolizine dihydropyranones were found to be unstable to column chromatography or decomposed within a short time of isolation. Therefore, it was anticipated that an *in situ* ring opening of the dihydropyranone would provide products that were inherently more stable. A number of nucleophiles were examined to both find a general method for the remaining substrate scope but to also showcase the number of derivatives that can be prepared quickly and efficiently using this method (Table 30). The simple procedure for conducting this ring opening involved adding an excess of

nucleophile with stirring at rt for a further 4-16 h. In all cases investigated, the corresponding products were obtained with excellent isolated yields and superb diastereo- and enantioselectivities. Ring opening with MeOH provided pyrrolizine **594** in 86% yield, >95:5 dr and >99% ee. Non-aromatic nitrogen-containing heterocycles are widespread in a number of commercial biologically active compounds. To show that these functional groups could be included into the pyrrolizine products the corresponding amines were used for the ring opening protocol. Pyrrolidine worked well with amide **595** produced in quantitative yield, >95:5 dr and >99% ee. Morpholine ring opens the intermediate dihydropyranone with **596** provided in 72% yield, >95:5 dr and >99% ee. The structurally related and important piperazine motif can be incorporated with **597** obtained in 72% yield, >95:5 dr and >99% ee. Allyl amine proved successful with amide **598** given in 81% yield, >95:5 and 97% ee and included the synthetically useful terminal alkene into the molecule. The tetrahydrothienopyridine structure is present in the compound Plavix®, a platelet aggregation inhibitor and one of the largest grossing pharmaceuticals on the market. This component could also be included into the pyrrolizine products with **599** produced in 60% yield, 95:5 dr and >99% ee.

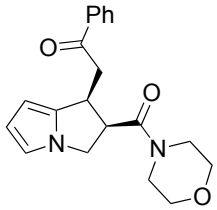




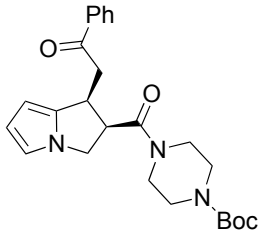
594
86% yield[a]
>95:5 dr[b], >99% ee[c]



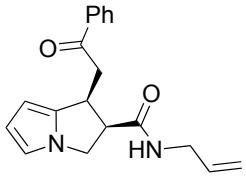
595
Quant. yield[a]
>95:5 dr[b], >99% ee[c]



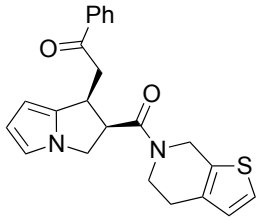
596
72% yield[a]
>95:5 dr[b], >99% ee[c]



597
72% yield[a]
>95:5 dr[b], >99% ee[c]



598
81% yield[a]
>95:5 dr[b], 97% ee[c]



599
60% yield[a]
95:5 dr[b], >99% ee[c]

[a]Isolated following column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Table 30 - Substrate scope: variation of nucleophile used for *in situ* ring opening.

Ring opening with allyl alcohol and propargyl alcohol appeared more difficult than with MeOH or amines. It was attempted to synthesise esters **600** and **601** as these molecules contain useful alkyne and alkene functional groups but even in the presence of DMAP (20 mol%) only trace ring opening occurred with pyrrolizine dihydropyranone returned (Table 31).

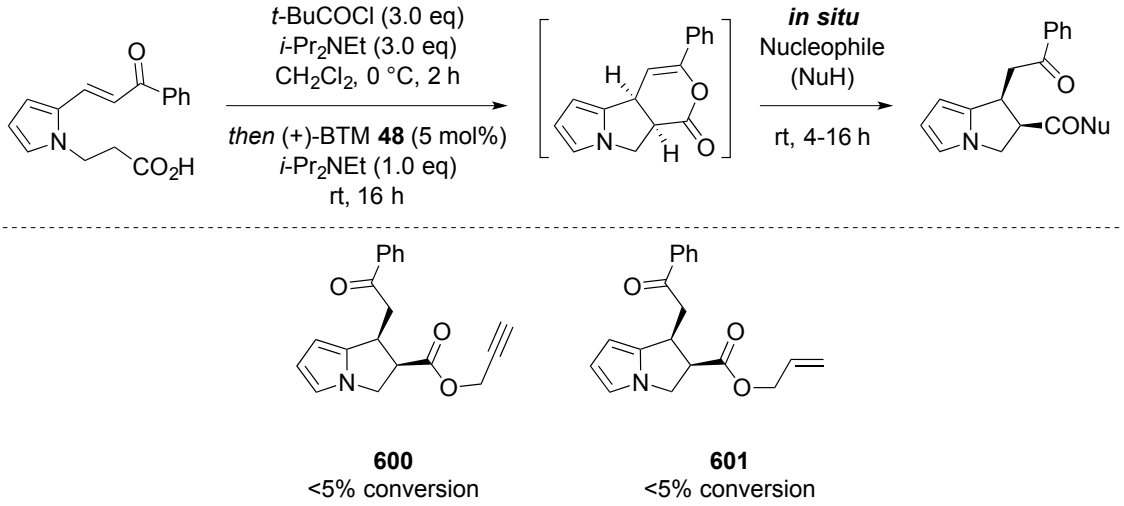
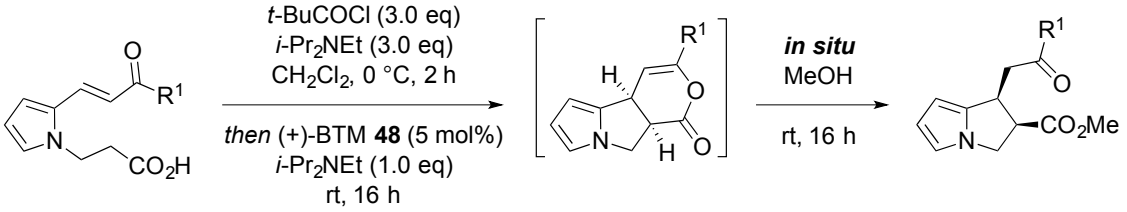
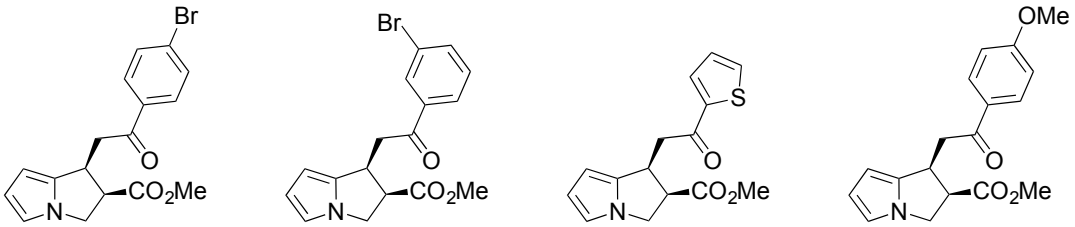


Table 31 - Substrate scope: unsuccessful ring openings.

6.4.2 Michael Addition-Lactonisation/Methanolysis Scope: Variation of Substrate

As methanol is a cheap, readily available commodity and proved highly successful in the ring opening procedure it was chosen as the standard nucleophile when investigating further pyrrolizine substrates (Table 32). Brominated aryl units can be included with products **602** and **603** produced in 78% and 74% yield, 99% and >99% ee, respectively and both as a single diastereoisomer. Heteroaromatic groups such as thiophene are tolerated with **604** accessed in 77% yield, >95:5 dr and 98% ee. Electron-rich aromatics such as the 4-$MeOC_6H_4$ unit worked well in the protocol with **605** achieved in 93% yield, >95:5 dr and >99% ee. The 2-Np and more sterically demanding 1-Np groups can both be incorporated with **606** and **607** produced in 81% and 68% yield respectively, with both achieved as single diastereoisomers and enantiomer. Unfortunately, the inclusion of alkyl groups did not prove successful with the application of pyrrolo enone-acid **563** showing no observable conversion into **609** with catalyst loadings of 5 mol% or 20 mol%.



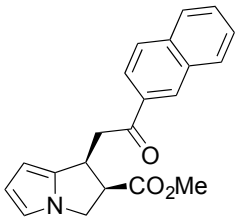


603
78% yield[a]
>95:5 dr[b], 99% ee[c]

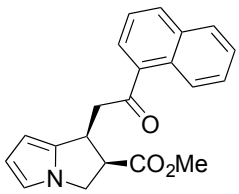
604
74% yield[a]
>95:5 dr[b], >99% ee[c]

605
77% yield[a]
>95:5 dr[b], 98% ee[c]

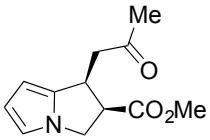
606
93% yield[a]
>95:5 dr[b], >99% ee[c]



607
81% yield[a]
>95:5 dr[b], >99% ee[c]



608
68% yield[a]
>95:5 dr[b], >99% ee[c]

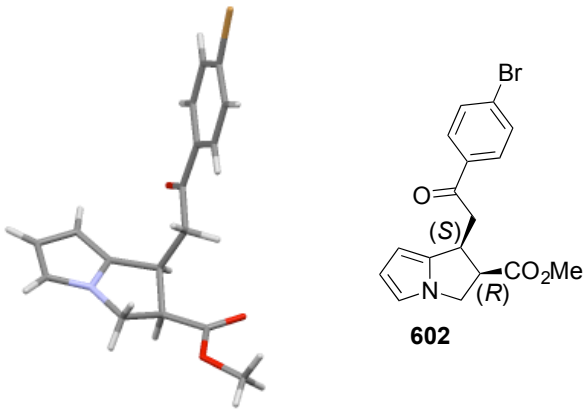


609
No observable conversion

[a]Isolated following column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Table 32 - Substrate scope: variation of pyrrolizine enone component.

The absolute configuration at the C(1) and C(2) position of **602** was confirmed by X-ray crystallography to be (1*S*,2*R*) (Figure 45). All other dihydropyranones were assigned by analogy.

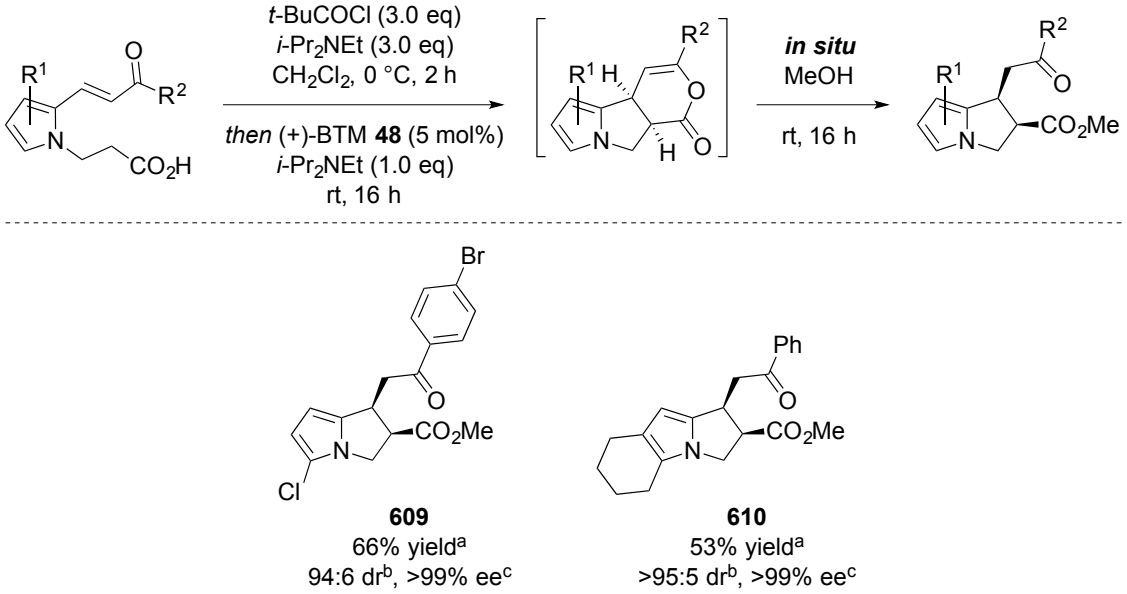


602

Figure 45 - X-ray crystal structure and molecular representation of 603.

Substrates **573** and **593** bearing elaborated pyrrole cores were next assessed. Chlorinated product **609** was isolated in 66% yield, 94:6 dr and >99% ee (Table 33).

Hexahydro-1*H*-pyrroloindole product **611** was prepared in moderate 53% yield, due to the use of crude substrate **593**, but with excellent >95:5 dr and >99% ee.

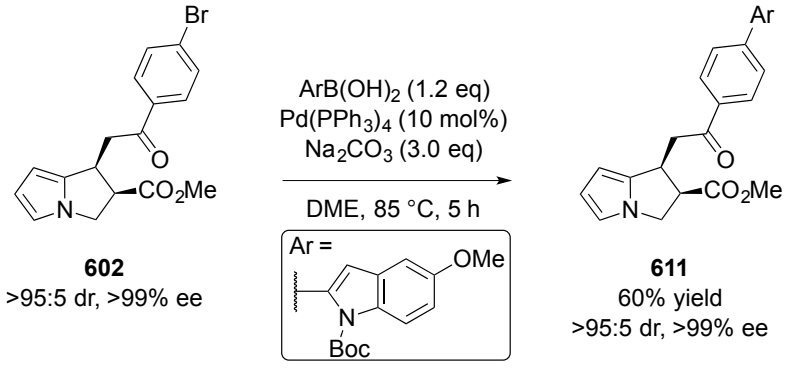


[a]Isolated following column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Table 33 - Substrate scope: variation of pyrrolizine core.

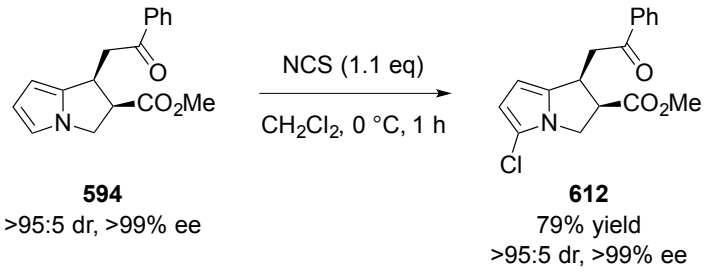
6.5 Derivatisation

To exemplify that this methodology could also be used as a basis for further synthetic steps, a selection of derivatisations were explored (Scheme 116). The synthesis of product **602** using this cascade methodology gives a product with the bromine functional handle. Through the use of the common and powerful Suzuki-Miyaura coupling this product can be further elaborated to access the polyheteroaromatic pyrrolizine **611** in 60% isolated yield and with no loss of dr or ee.[143]



Scheme 116 - Suzuki-Miyaura coupling.

Furthermore, a simple chlorination of the pyrrolizine **594** core can be conducted using *N*-chlorosuccinimide to access chloropyrrolizine **612** in 79% yield with the incorporation of a further functional handle (Scheme 117).



Scheme 117 - Pyrrolizine chlorination reaction.

6.6 Computational Studies and Stereochemical Rationale

6.6.1 Proposed Mechanism

This process is believed to start with formation of mixed anhydride **613** *in situ* from the starting pyrrolo enone-acid, pivaloyl chloride and *i*-Pr_2NEt. *N*-acylation by isothiourea catalyst **48** gives intermediate acyl ammonium **614** that, following deprotonation, provides (*Z*)-ammonium enolate **615** (Figure 46). Enantiodetermining intramolecular Michael addition gives pyrrolizine intermediate **616** that undergoes lactonisation to provide pyrrolizine dihydropyranone **617** and regenerate the catalyst. *In situ* ring opening of **617** with a nucleophile gives the *syn*-pyrrolizine product **618**.

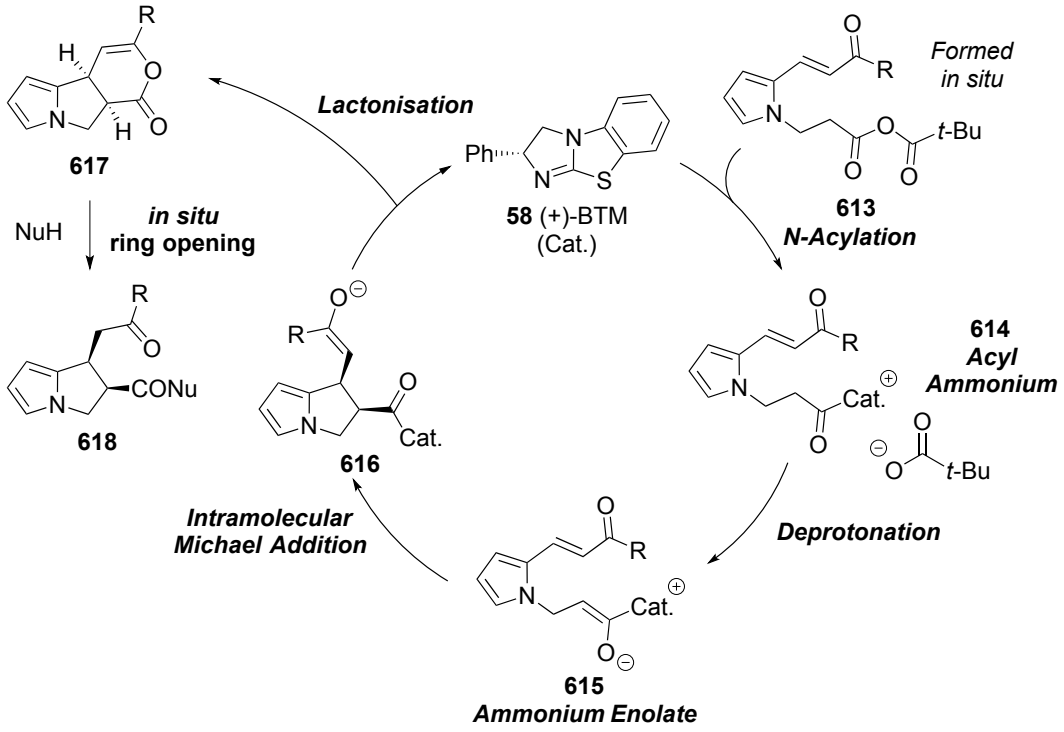


Figure 46 - Proposed reaction mechanism.

6.6.2 Computational Studies

In collaboration with Professor Stuart Macgregor at Heriot Watt University, a computational study of the reaction profile and analysis of the reaction stereoselectivity was conducted.[144] Calculations were run with Gaussian 09 Revision D.01[145] with PCM solvent corrections run with Gaussian 09, Revision D.01[146] Geometry optimisations were performed using the M06-2X functional[147] using 6-31G** basis sets[148] on all atoms (called BS1). All stationary points were fully characterized via analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue) and IRC calculations and subsequent geometry optimisations were used to confirm the minima linked by each transition state. Frequency calculations also provided a free energy in the gas-phase, computed at 298.15 K and 1 atm. SCF energies were recomputed with the larger 6-311++G** basis set[149] (BS2) and incorporate a correction for CH_2Cl_2 solvent (CH_2Cl_2, PCM approach[150]).

Firstly, the reaction pathways leading to the *cis*-isomer, observed as the major product of the reaction, and the possible *trans*-isomer were modelled (Figure 47a and b). The modelling for the *cis*-pathway started with the (*Z*)-ammonium enolate **R1** proceeding *via* the Michael addition transition state $\mathbf{TS1_{cis}}$ (+5.1 kcalmol^{-1}) into *cis*-intermediate $\mathbf{Int_{cis}}$ (−0.6 kcalmol^{-1}). Cyclisation occurs through $\mathbf{TS2_{cis}}$ (6.5 kcalmol^{-1}) to provide ring-closed intermediate $\mathbf{Int2_{cis}}$ (1.7 kcalmol^{-1}). Elimination of the (+)-BTM catalyst gives pyrrolizine dihydropyranone product $\mathbf{P_{cis}}$ (−18.2 kcalmol^{-1}) with the catalyst closely associated. The reaction pathway leading to the two possible *trans*-isomers was modelled using the same reaction sequence starting from (*Z*)-ammonium enolate **R1** or (*E*)-ammonium enolate **R2** leading to the *trans*-products $\mathbf{P_{trans\text{-}1}}$ and $\mathbf{P_{trans\text{-}2}}$, respectively. The key features present in these reaction profiles are the significantly smaller overall barrier of the *cis*-pathway (6.5 kcalmol^{-1}) compared to the *trans*-pathways (16.6 kcal^{-1} when starting from (*E*)-enolate and 9.9 kcalmol^{-1} when starting from the (*Z*)-enolate). This suggests that the reaction proceeds under kinetic control.

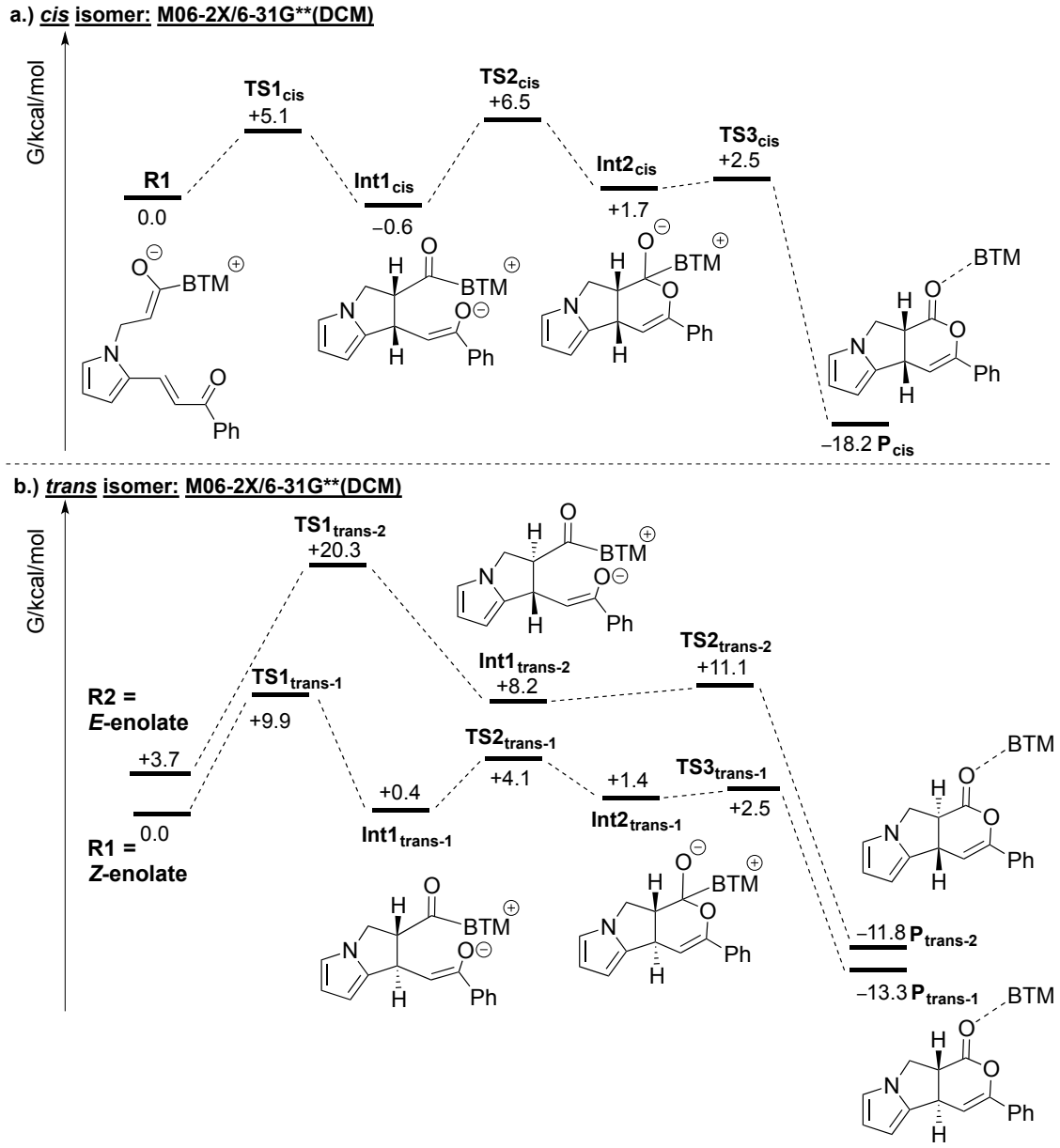
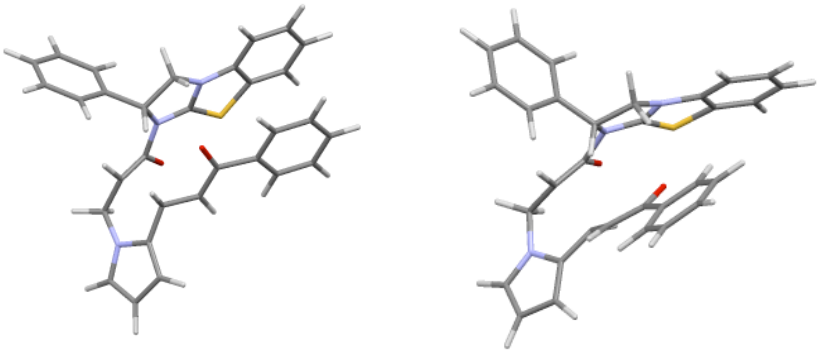


Figure 47 - Calculated reaction pathways for formation of the a.) *cis*-isomer and the b.) *trans*-isomers using M06-2X(BS2, DCM)//M06-2X(BS1).

One contributing factor for the lower energy barrier of the $\mathbf{TS_{cis}}$ versus the $\mathbf{TS_{trans\text{-}1}}$ may be explained by the favourable π-stacking interaction between catalyst and the aryl substituent situated on the enone component (Figure 48). Modelled $\mathbf{TS_{cis}}$ shows these groups to be located in favourable conformation aiding this interaction (inter-plane angle = 5.7°). However, in $\mathbf{TS_{trans\text{-}1}}$ the conformation is more strained with the catalyst and phenyl substituent on the enone aligned in different planes (inter-plane angle = 28.1°) and hence minimising a potential π-stacking interaction.



TS1$_{cis}$ (5.1 kcalmol^{-1}) **TS1$_{trans-1}$** (9.9 kcalmol^{-1})

Figure 48 - Calculated transition structures for the Michael addition step leading to the *cis*- and *trans*-isomers.

To rationalise the diastereo- and enantioselectivity observed in this process, the calculated transition state **TS$_{cis}$** can be used as a basis. Following generation of the (*Z*)-ammonium enolate the intramolecular Michael addition occurs with the two protons placed in a *syn*-orientation with enone and enolate positioned pseudoequatorial (Figure 49). Reaction proceeds with nucleophilic attack at the *Re*-face of the enone leading to the formation of the (4a*S*,9a*R*)-enantiomer of the final pyrrolizine dihydropyranone, following lactonisation. A favourable stereoelectronic interaction between the sulfur of the catalyst and oxygen of the enolate is believed to rigidify this assembly, as described already for related isothiourea-catalysed processes. This 1,5 oxygen to sulfur interaction appears to be present throughout all calculated Michael addition transition states with the enolate oxygen and catalyst sulfur observed to be in a *syn*-coplanar conformation. Moreover, this distance is found to be 0.579 Å shorter than the predicted van der Waals radii (3.320 Å) suggesting this interaction to be significant.[37]

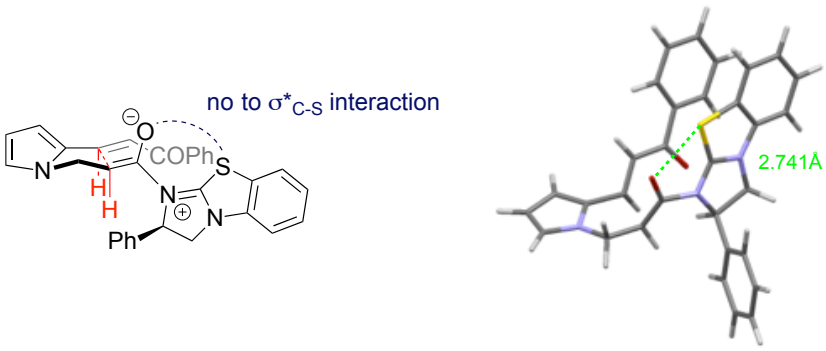
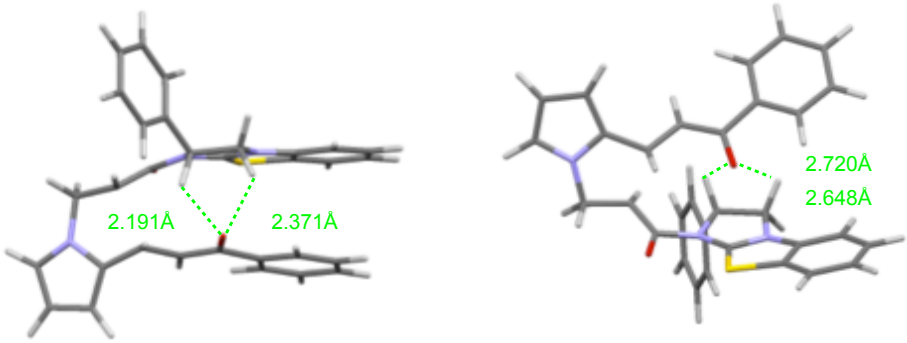


Figure 49 - Proposed diastereo- and enantioselectivity rationale. Molecular representation and calculated TS1$_{cis}$ (M06-2X(BS2, DCM)//M06-2X(BS1)).

Another potential feature in **TS1$_{cis}$** is the close proximity of the enone oxygen and the catalyst C(2) and C(3) protons (Figure 50). The interatomic distances of 2.191 Å (C(2)H---O)

and 2.371Å (C(3)H---O) suggest that a non-classical H-bonding interaction is possible with potential stabilising effects. A contributing factor here may be the positioning of the C(2)H and C(3)H adjacent to the isothiouronium core of the catalyst. This may therefore increase the acidity of these C−H bonds and consequently allow them to become stronger H-bonding donors. Although not significantly strong individually these stabilising contacts may impart influence on the high selectivity for the observed stereoisomer. It should be noted that the equivalent contacts in the $\mathbf{TS_{trans\text{-}1}}$ structure are somewhat longer (2.720 Å and 2.648 Å) and therefore suggesting that this interaction is less significant in the *trans*-pathway compared to the *cis*-pathway.



$\mathbf{TS1_{cis}}$ $\mathbf{TS_{trans\text{-}1}}$

Figure 50 - Calculated $\mathbf{TS1_{cis}}$ and $\mathbf{TS_{trans\text{-}1}}$ (M06-2X(BS2, DCM)//M06-2X(BS1)) with measured intramolecular O---H bond distances.

6.7 Conclusions

An enantioselective synthesis of pyrrolizines *via* an isothiourea-catalysed Michael addition-lactonisation process has been established. An efficient and reproducible route to prepare a range of pyrrolo enone-acid substrates has been was discovered with products obtained in good overall yield. Activation *in situ* of the pyrrolo enone-acids to a mixed anhydride using pivaloyl chloride and *i*-Pr_2NEt is first conducted with the introduction of catalyst (+)-BTM **48** (5 mol%) gives pyrrolizine dihydropyranone species with a wide selection of amines or MeOH used to ring open these intermediates giving pyrrolizine products with exquisite diastereo- and enantioselectivity (>95:5 dr and 97-99% ee). Derivatisation of the pyrrolizine products has been demonstrated to show the utility of these compounds with no loss of the high dr or ee. Computational experiments indicate that the reaction for the formation of the observed *syn*-diastereoisomer to be under kinetic control with the *syn*-product also calculated to be lower in energy than either possible *anti*-product.

6.8 References and Notes

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Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 7: Application of Saccharin-Derived Substrates in Isothiourea-Catalysis

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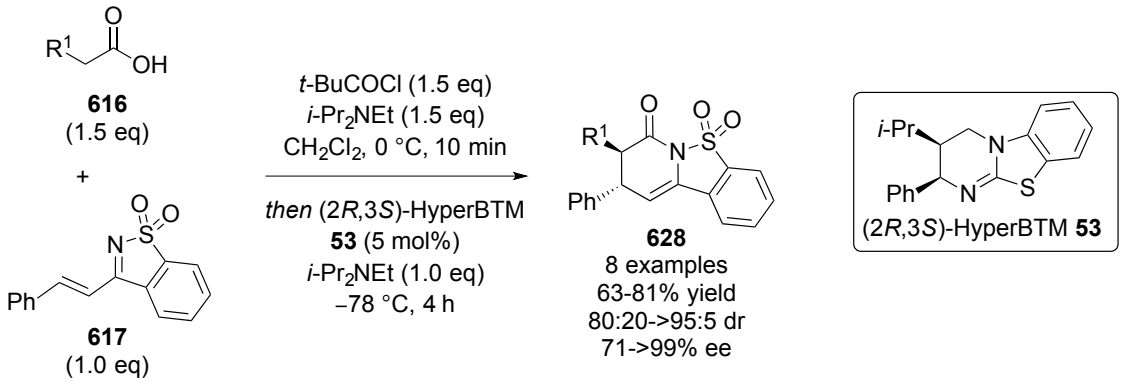
Chapter 7: Application of Saccharin-Derived Substrates in Isothiourea-Catalysis

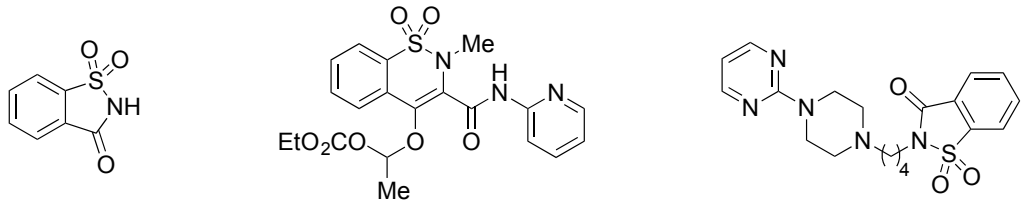
This chapter describes the discovery of an enantioselective organocatalytic methodology for the synthesis of chiral 8,9-dihydro-7*H* benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxides with high stereocontrol. This optimised process consists of a (2*R*,3*S*)-HyperBTM **53** (5 mol%)-catalysed Michael addition-lactamisation using cyclic sulfonyl imines **617** derived from saccharin and commercially available carboxylic acids **616**, giving the sultam products **618** in typically excellent diastereo- and enantiocontrol (Scheme 118).



Scheme 118 - Enantioselective isothiourea-catalysed synthesis of 8,9-dihydro-7*H* benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxides

7.1 Introduction

Saccharin (1,2-benzisothiazol-3-one 1,1-dioxide) **619** is a synthetic calorie-free additive, widely used as sugar substitute in many food products and has proven an important discovery in the fight against diabetes.[151] However, the cyclic sulfonamide core structure has also attracted much interest in recent decades from the medicinal chemistry community. It is now well known that sulfonamides, and specifically cyclic sulfonamides (sultams), are key constituents in many biologically active drugs such as Ampiroxicam **620**,[152] a member of a large family of nonsteroidal anti-inflammatory agents (Figure 51). In particular, saccharin-based sultams have been found to be active agonists of 5-HT_{1A} receptors and have therefore been applied as neuroprotectants or anxiolytics such as that of Ipsaspirone **621**.[153] Current research within this area has led to the development of saccharin derivatives as inhibitors of carbonic anhydrase enzymes.[154]



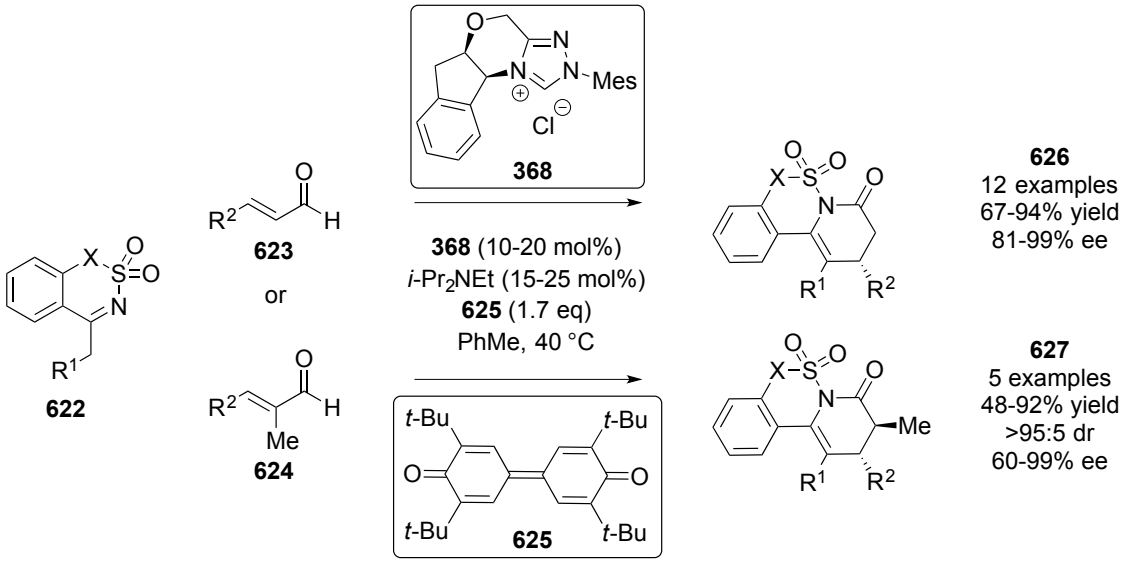
Saccharin 619
Calorie-free sugar surrogate

Ampiroxicam 620
Non-steroidal anti-imflammatory agent

Ipsapirone 621
$5HT_{1A}$ receptor agonist
Antidepressant and anxiolytic effects

Figure 51 - Saccharin and biologically relevant saccharin derivatives.

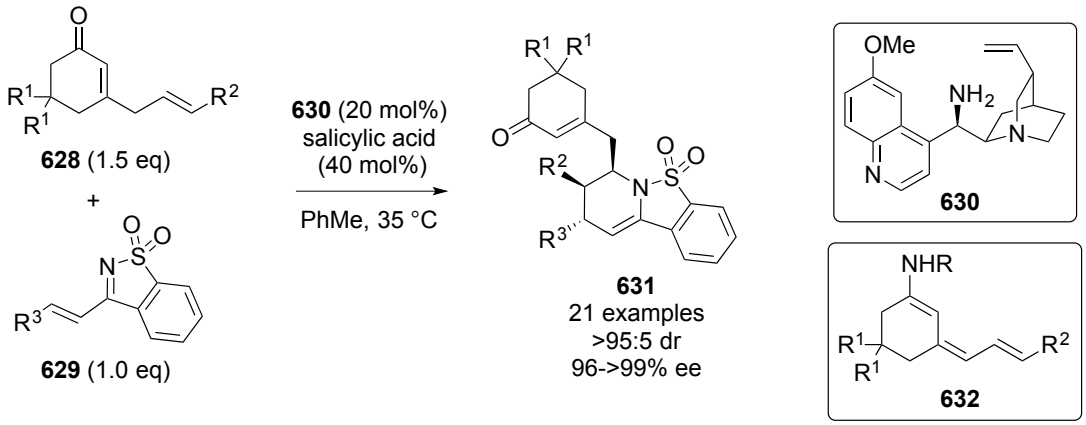
With the growing medicinal interest in saccharin-derived sultams it is no wonder that a number of methodologies have appeared to provide efficient synthetic routes into these compounds. In particular, a number of enantioselective organocatalytic strategies have been explored to access chiral sultam products with stereocontrol. One such example was report in 2012 from Bode and co-workers using NHC acyl azolium catalysis in an annulation process (Scheme 119).[155] Sulfonyl imine **622**, prepared in one-step from saccharin, was treated with enal **623**, NHC **368** (10 mol%), *i*-Pr_2NEt and oxidant **625** giving tricylic sultams **626** in good to excellent yield (67-94%) and excellent enantioselectivity (81-99% ee) when monosubstituted enals were applied. A select few enals containing disubstitution were also tested with sultams **627** produced as single diastereoisomers (>95:5 dr) with moderate to excellent enantioselectivity (60-99% ee).



Scheme 119 - NHC-catalysed annulation of enals and imines *via* α,β-unsaturated acyl azoliums.

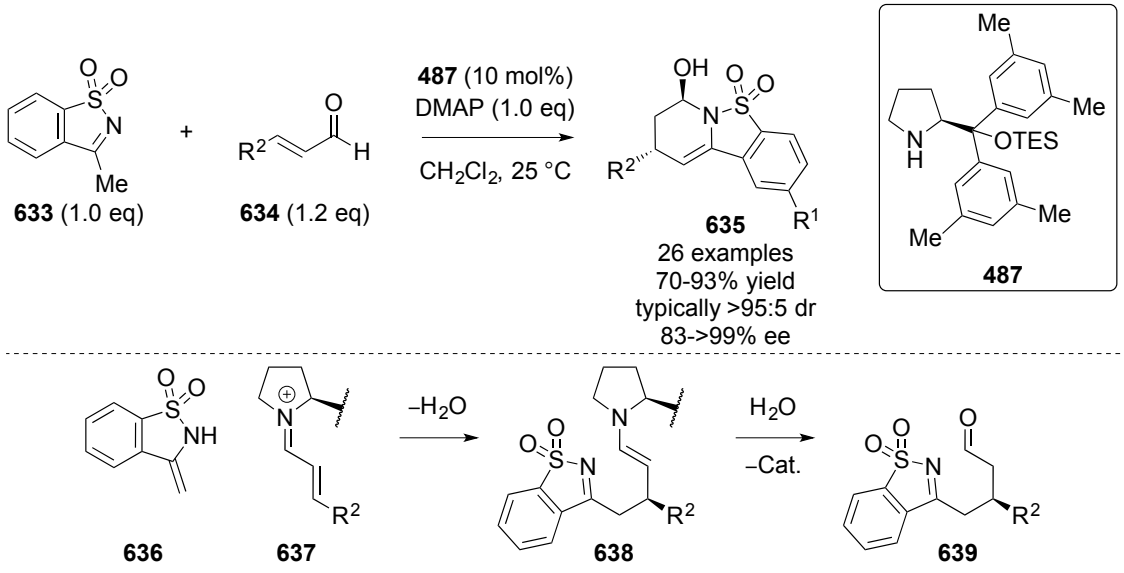
Another organocatalytic approach, this time from Chen and co-workers in 2014 investigated an aza Diels-Alder reaction using organocatalytically generated trienamines (Scheme 120).[156] Reaction of ketones **628**, cyclic sulfonyl imine **629** and cinchona alkaloid **630** (20 mol%) in the presence of salicylic acid generates trienamine intermediate **632** which can

react through the δ,ε-alkene in an inverse electron demand Diels-Alder reaction with cyclic sulfonyl imines **629** to give products **631** in excellent diastereo- and enantioselectivity (>95:5 dr and 96->99% ee).



Scheme 120 - Enantioselective synthesis of sultams using enamine catalysis.

In 2015, Chen and co-workers utilised iminium catalysis with an asymmetric tandem synthesis of saccharin-derived sultams. Reaction of sulfonyl imines **633**, prepared in one-step from saccharin, with enals **634** in the presence of catalyst **487** (10 mol%) and DMAP (1.0 eq) gives hydroxy sultams **635** typically excellent diastereoselectivity (>95:5 dr) and enantioselectivity (83->99% ee) (Scheme 121). It is proposed that following the formation of iminium intermediate **637** and tautomerisation of **633** that this reaction pair can undergo a Michael addition step to give **638**. After tautomerisation and hydrolysis of **638**, the intermediate **639** cyclises to give the observed products.



Scheme 121 - Michael addition-cyclisation reaction for the synthesis of sultams using iminium catalysis.

It is evident that the synthesis of chiral sultams is of high importance in organic chemistry with new methodologies to prepare such molecules still required. Based upon the previous Smith group work in the area of enantioselective Michael addition-lactamisation cascades it was proposed that saccharin-derived Michael acceptors might prove suitable for such a process (Figure 52). Reaction with isothiourea-generated enolate equivalents would therefore provide access to stereodefined 8,9-dihydro-7H benzo[4,5]isothiazolo[2,3-a]pyridin-7-one-5,5-dioxides moieties.

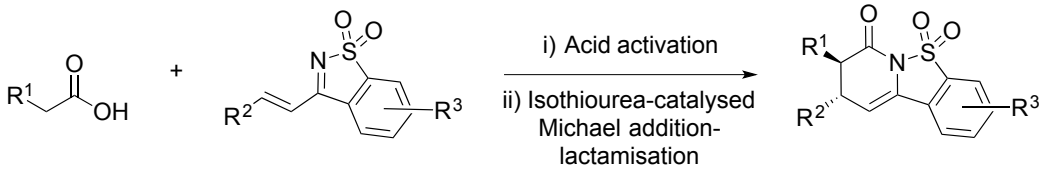
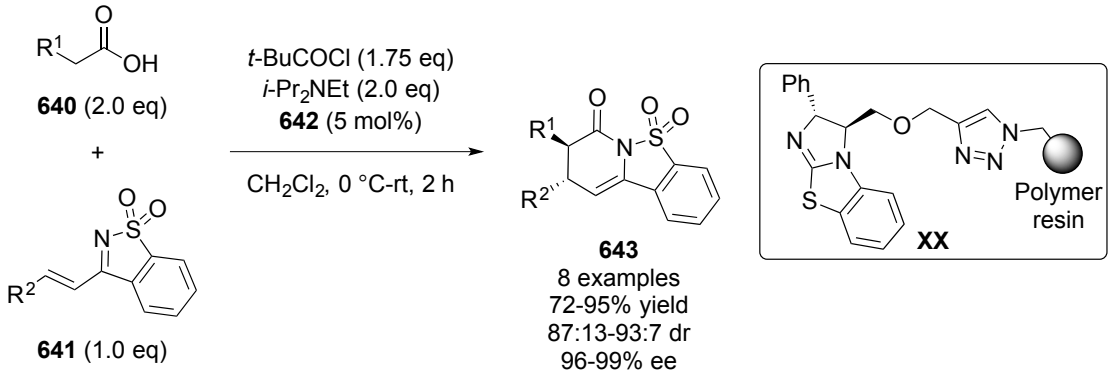


Figure 52 - Proposed project plan.

It should be noted that during the course of this project a similar reaction process by Pericàs and co-workers was reported. Here the authors report a Michael addition-lactamisation protocol using carboxylic acids **640** as enolate precursors, Michael acceptors **641** and a polymer supported (+)-BTM catalyst **48** (15 mol%) (Scheme 122).[157]

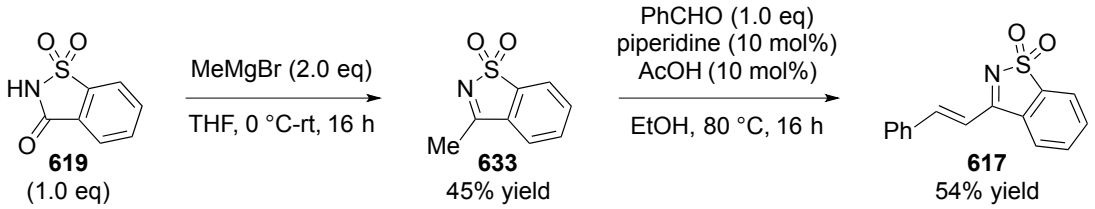


Scheme 122 - Related protocol reported during the undertaking of this project.

7.2 Enantioselective Michael Addition-Lactamisation

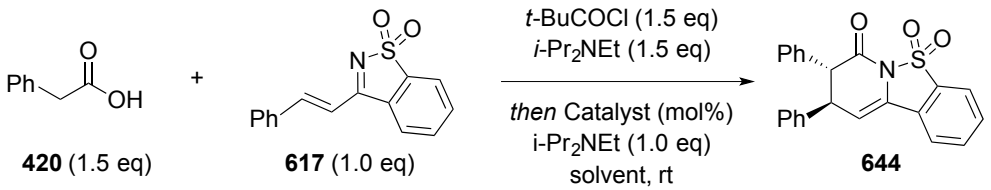
7.2.1 Initial Reaction Optimisation

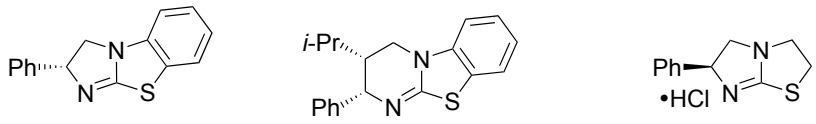
The cyclic sulfonyl imine was chosen as a model system that would assess the optimisation of the reaction and was prepared using the procedure by Chen and co-workers (Scheme 123).[156] The process starts with cheap and commercially available saccharin **619** with addition of MeMgBr and dehydration to give imine **633** in moderate yield after recrystallisation (45%). **633** is subjected to an aldol reaction with benzaldehyde, piperidine and acetic acid to provide α,β-unsaturated cyclic sulfonyl imine **617** in moderate yield (54%).



Scheme 123 - Synthetic route to prepare saccharin-derived Michael acceptors.

The optimisation studies began with a isothiourea catalyst screen using the carboxylic acid activation protocol described previously (Table 34). Reaction conducted with (2*S*,3*R*)-HyperBTM **53** (10 mol%) at rt gave the desired product **644** 64% yield, 84:16 dr and 79% ee. (+)-BTM **48** (10 mol%) catalysed reaction gave **644** in slightly improved 71% yield, 85:15 dr and 83% ee. The optimum catalyst, however, was found to be (−)-tetramisole•HCl **47** (10 mol%) giving tricyclic sultam **644** in 73% yield, 85:15 dr and excellent 95% ee. It was attempted to lower the catalyst loading to 5 mol% but this led to a reduced 56% yield isolated yield, 83:17 dr and 88% ee. It was observed in this case that the reaction time was longer (4 h) and it is likely some starting material or product began to decompose over this time, explaining the reduced yield. It can also be suggested that the lower stereoselectivity originates from a more dominant racemic background reaction in the presence of lower catalyst concentrations. Different solvents such as EtOAc, THF and toluene were tested with poorer results obtained overall and a poor solubility in toluene leading to a low conversion.





Entry	Catalyst (mol%)	Solvent	Yield (%)[a]	dr[b]	ee (%)[c]
1	**48** (10)	CH_2Cl_2	64	84:16	79 (ent)
2	**53** (10)	CH_2Cl_2	71	85:15	83 (ent)
3	**47** (10)	CH_2Cl_2	75	86:14	95
4	**47** (5)	CH_2Cl_2	65	85:15	95
5	**47** (2)	CH_2Cl_2	56	86:14	88
5	**47** (10)	EtOAc	65	85:15	84
6	**47** (10)	THF	61	85:15	85
7	**47** (10)	PhMe	16	85:15	84

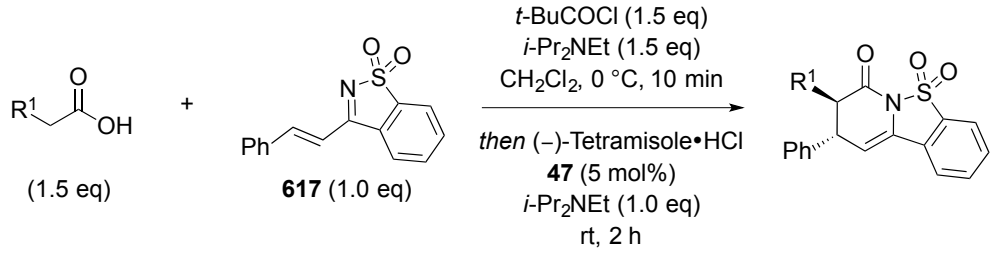
[a]Isolated following column chromatography using Biotage® Isolera™ 4. [b]Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [c]Determined by chiral HPLC analysis.

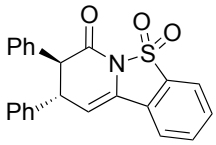
Table 34 - Reaction optmisation.

With such good results obtained for the (−)-tetramisole•HCl **47** reaction, these conditions were carried forward into the assessment of the substrate scope.

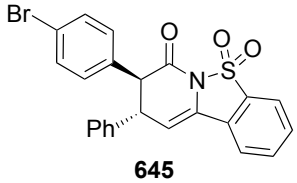
7.2.2 Substrate Scope and Further Reaction Optimisation

The first task in evaluating the reaction substrate scope was to assess a range of commercially available carboxylic acids using the cyclic sulfonyl imine substrate **617** (Table 35). Through assessing the scope of carboxylic acids it was observed that many of the products were achieved in poor enantioselectivity. For example the reaction with 4-bromophenyl acetic acid gave sultam **645** in a moderate 61% ee. *o*-Tolyl acetic acid and (*E*)-4-phenylbut-3-enoic acid gave the corresponding products **647** and **651** in poor 50% ee. Application of 3-thiophene acetic acid yielded the thienyl sultam product **646** in an excellent 90% ee but in a moderate 74:26 dr. It became apparent that the range of results was broad and in most cases selectivities were mediocre. Crude reaction mixtures in all examples were found to be promising (as determined by ^{1}H NMR analysis) with only the desired product and a small amount of decomposition material observed. However, the isolated yields obtained were in a moderate to good range (58-72%), thus not reflecting the analysis of the crude reaction or the expected mass return after purification. Treatment of **644** to a solution of silica gel in EtOAc:hexane (20:80) and stirring for 1 h led to significant decomposition and suggests that instability to column chromatography is the cause of the reduced yields.

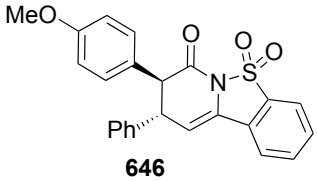




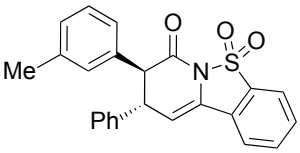
644
65% yield[a]
85:15[b] (85:15)[c] dr
95% ee[d]



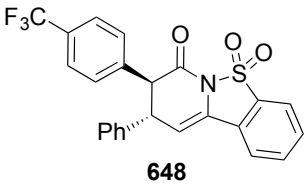
645
72% yield[a]
90:10[b] (>95:5)[c] dr
61% ee[d]



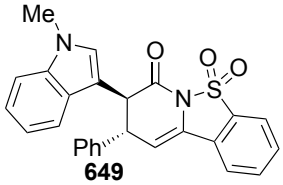
646
65% yield[a]
90:10[b] (90:10)[c] dr
89% ee[d]



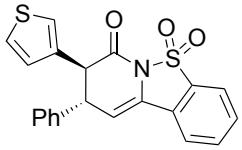
647
64% yield[a]
90:10[b] (90:10)[c] dr
50% ee[d]



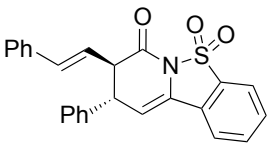
648
59% yield[a]
94:6[b] (>95:5)[c] dr
81% ee[d]



649
63% yield[a]
89:11[b] (89:11)[c] dr
70% ee[d]



650
66% yield[a]
74:26[b] (74:26)[c] dr
90% ee[d]

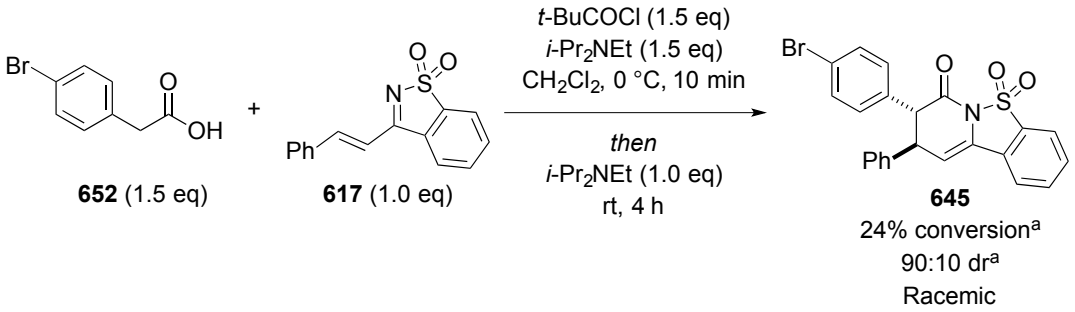


651
58% yield[a]
>95:5[b] (>95:5)[c] dr
50% ee[d]

[a]Isolated by column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by ^{1}H NMR spectroscopic analysis of isolated mixture. [d]Determined by chiral HPLC analysis.

Table 35 - Substrate scope: variation of carboxylic acid using (−)-Tetramisole•HCl 47 at rt.

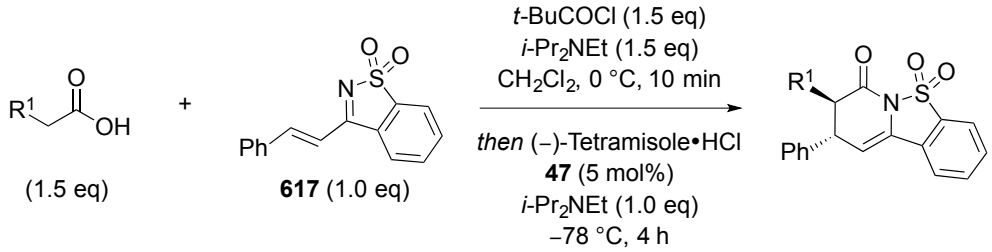
With the poor results obtained above it was clear that the initial optimum conditions were not general and that further optimisation was required. To explain the moderate enantioselectivity a control reaction conducted in the absence of the chiral Lewis base catalyst was undertaken (Scheme 124). Treatment of 4-bromophenyl acetic acid **652** with pivalolyl chloride, *i*-Pr$_2$NEt and Michael acceptor **616** gave 24% conversion into corresponding product **644** (as determined by ^{1}H NMR spectroscopic analysis). Although only a small conversion, this evidence implies that a racemic base-mediated background reaction between the mixed anhydride formed *in situ* and **617** is possible and offers competition to that of the enantioselective process.

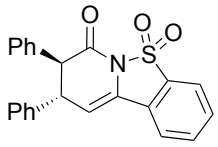


[a]Determined by ^{1}H NMR spectroscopic analysis of crude mixture.

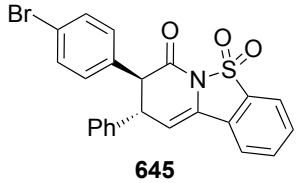
Scheme 124 - Control reaction in the absence of isothiourea catalyst.

To minimise the competition from the racemic background reaction the reaction temperature was lowered to −78 °C. All of the same carboxylic acid substrates were investigated again as it was believed that a broader overview of the obtained results was necessary to assess the generality of this protocol as opposed to optimisation of a single substrate (Table 36). First of all, the ^{1}H NMR spectra obtained for all crude reaction mixtures proved cleaner at −78 °C with only products and a small amount of decomposition material. This cleaner reaction mixture allowed for a greater eluent polarity to be used in the column chromatography purification thus minimising the exposure time of the products to silica gel and overall leading to improved isolated yields (61-80%). However, the simplified chromatographic purification made the separation of the corresponding diastereoisomers difficult. Generally, enantioselectivity was also improved with examples such as showing enantiomeric excesses 5-15% higher than that observed following the rt reaction. Products **644**, **646** and **650** remained in high selectivity although (95->99% ee); many of the sultams were accessed in what was still considered moderate enantiocontrol (50-86% ee).

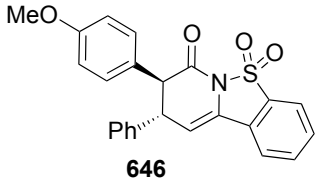




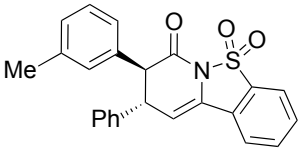
644
65% yield[a]
85:15[b] (85:15)[c] dr
95% ee[d]



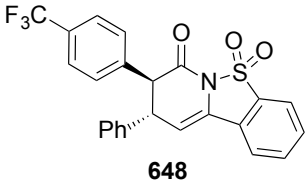
645
80% yield[a]
90:10[b] (>95:5)[c] dr
81% ee[d]



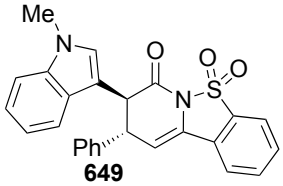
646
74% yield[a]
90:10[b] (90:10)[c] dr
98% ee[d]



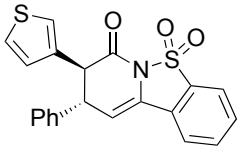
647
70% yield[a]
90:10[b] (90:10)[c] dr
60% ee[d]



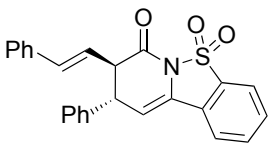
648
64% yield[a]
94:6[b] (>95:5)[c] dr
86% ee[d]



649
62% yield[a]
89:11[b] (89:11)[c] dr
85% ee[d]



650
78% yield[a]
74:26[b] (74:26)[c] dr
>99% ee[d]



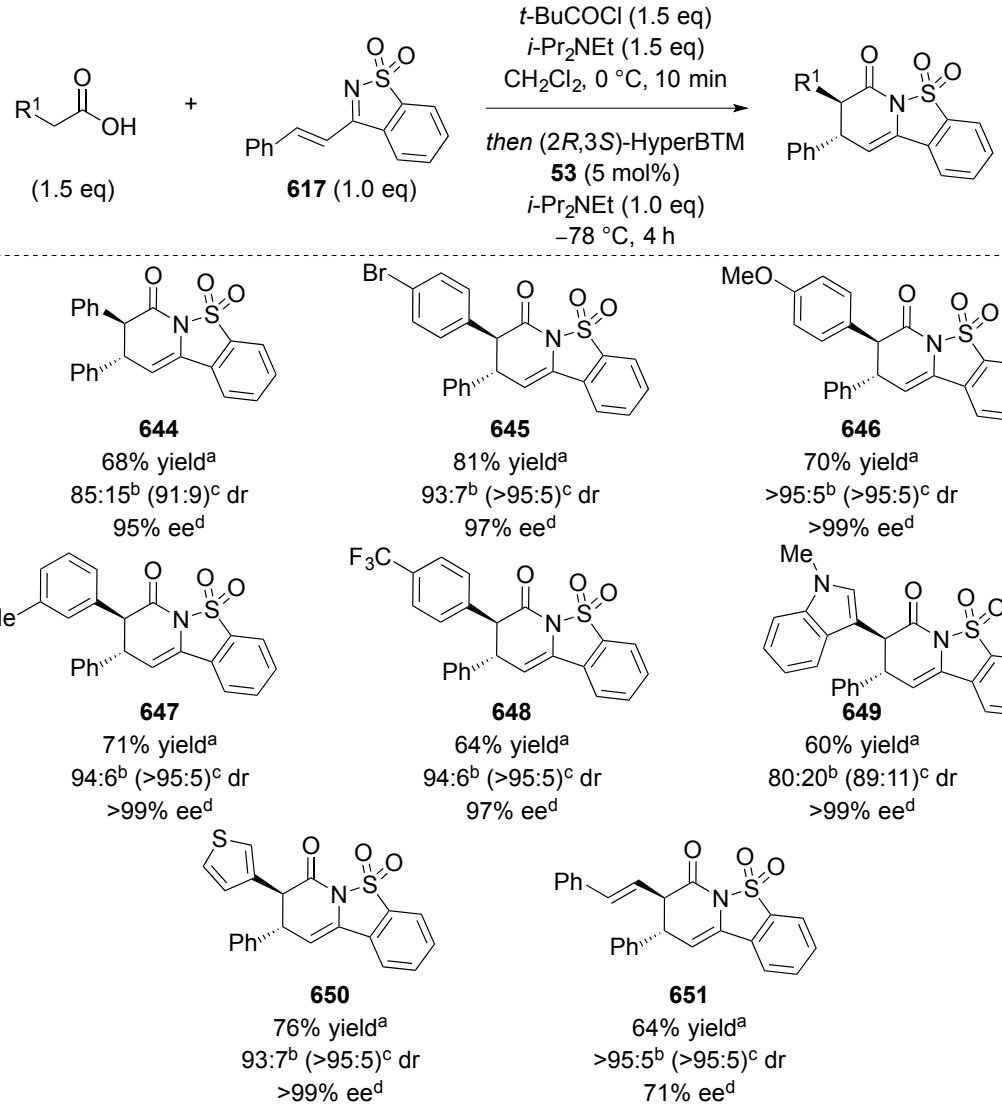
651
61% yield[a]
>95:5[b] (>95:5)[c] dr
50% ee[d]

[a]Isolated by column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by ^{1}H NMR spectroscopic analysis of isolated mixture. [d]Determined by chiral HPLC analysis.

Table 36 - Substrate scope: variation of carboxylic acid using (−)-Tetramisole•HCl 47 at −78 °C.

A new catalyst screen was undertaken at the lowered reaction temperature of −78 °C (Table 37). (+)-BTM **48** (5 mol%) offered poorer results to that of (−)-Tetramisole•HCl **47** (5 mol%) and was therefore not pursued. Pleasingly, however, (2*R*,3*S*)-HyperBTM **53** (5 mol%) proved significantly more successful. Brominated sultam **645** was produced in 81% yield, 93:7 dr and excellent 97% ee. Sultam **646** incorporating the electron rich 4-MeOC_6H_4 substituent was now achieved in 70% yield, >95:5 dr and >99% ee. Dramatic improvements in enantioselectivity was observed with products **647** and **648** provided in >99% and 97% ee, respectively. Indole containing product **651** also showed a significant increase in enantioselectivity with **649** prepared in 64% 80:20 dr and >99% ee. An improvement was recorded in the case of alkenyl example **651** but with still a moderate 71% ee obtained. Almost

all products showed excellent diastereoselectivities that led to the successful isolation of a single diastereoisomer in most cases.



[a]Isolated by column chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixture. [c]Determined by ^{1}H NMR spectroscopic analysis of isolated mixture. [d]Determined by chiral HPLC analysis.

Table 37 - Substrate scope: variation of carboxylic acid using (2*R*,3*S*)-HyperBTM 53 at −78 °C.

7.3 Reaction Mechanism

The reaction mechanism is believed to proceed similarly to that of the isothiourea-catalysed process already described in this thesis which begins with *N*-acylation of isothiourea catalyst from *in situ* formed mixed anhydride **652** to form an acyl ammonium species **653** (Figure 53). Subsequent deprotonation gives (*Z*)-ammonium enolate **654**, which undergoes an enantioselective Michael addition in the presence of **617**. Finally, lactamisation provides the corresponding sultam products **656** and releases the catalyst.

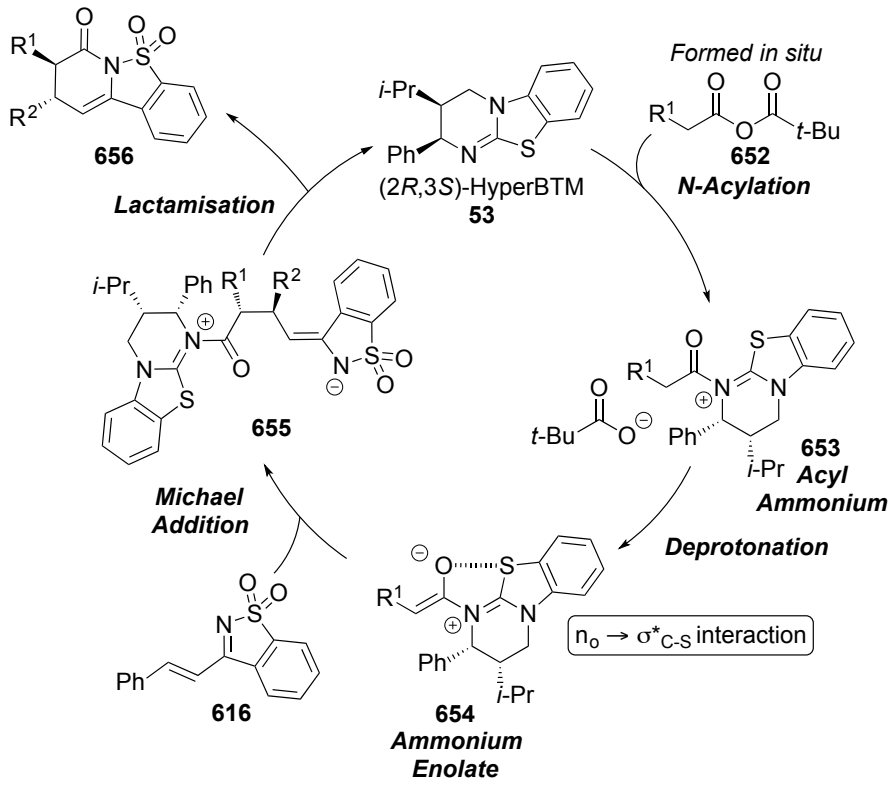


Figure 53 - Proposed reaction mechanism.

Rationalisation of the observed enantioselectivity in the Michael addition-lactamisation reaction can be based upon the results of related systems.[42] Ammonium enolate forms with a (*Z*)-configuration, stabilised by either an enolate oxygen and the C−S *anti*-bonding orbital (n_o to σ^*_{C-S}) interaction or a favourable electrostatic interaction (Figure 54).[36-37, 101] This interaction is believed to rigidify **657** with the Ph directing group from catalyst **53** adopting a pseudo-axial orientation and the *i*-Pr group positioned pseudoequitorial, thus blocking one face of the ammonium enolate. Inputting cyclic sulfonyl imine **617** into this model, the next stage is the enantiodetermining Michael addition that can be assigned by analogy to the Heathcock model giving **658**.[158] The adduct formed can then undergo lactamisation with substitution of the catalyst to provide *anti*-sultam (8*S*,9*S*)-**659**. The stereochemistry of all products was assigned by analogy to products produced from related isothiourea-catalysed processes.

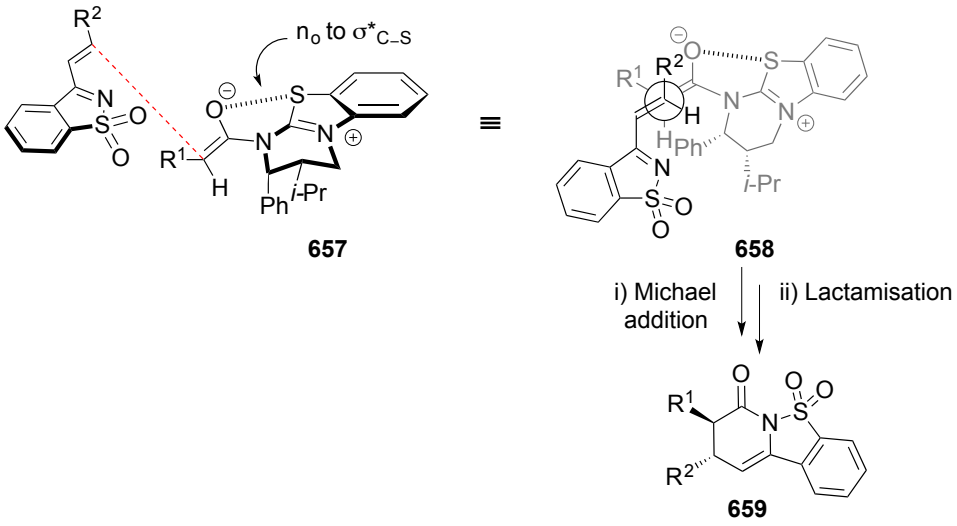
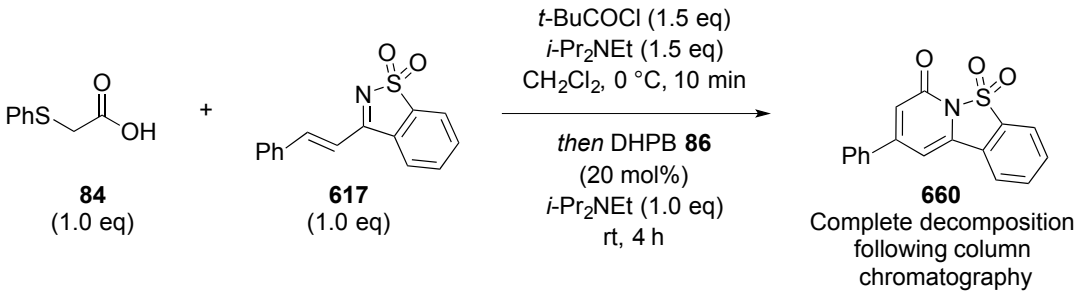


Figure 54 - Proposed stereochemical rationale.

7.4 One-Pot Michael Addition-Lactamisation/PhSH Elimination

It was envisioned that a further application of saccharin-derived Michael acceptors was to that of the isothiourea-catalysed Michael addition-lactamisation/PhSH elimination protocol, similar to that described in Chapter 2. This methodology would therefore provide a synthetic route to prepare the achiral 1,2-benzoisothiazole pyridone-1,1-dioxide molecules.

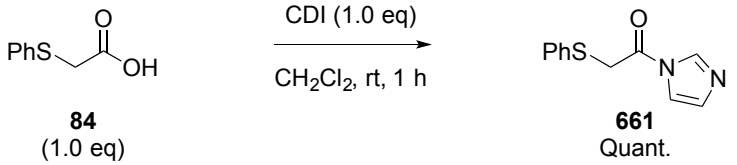
Starting from the procedure applied in the synthesis of pyridines (Chapter 2), (phenylthio)acetic acid **84** was treated with pivalolyl chloride, *i*-Pr_2NEt and Michael acceptor **617** in the presence of DHPB **86** (20 mol%) gave desired product **660** after 4 h (Scheme 125). This reaction led to **660** as the only reaction product and a typically promising crude reaction mixture (as determined by ^1H NMR analysis). Unfortunately, **660** was found to be very unstable to column chromatography with complete decomposition when exposed to silica gel.



Scheme 125 - Michael addition-lactamisation/PhSH elimination protocol.

With such a promising and efficient reaction occurring in this system it was therefore necessary to find an alternative purification method to access **660** successfully. As the product appeared to be solid, recrystallisation from Et_2O was attempted, but provided **660** at an unsatisfactory level of purity. To simplify the system and therefore make the purification by recrystallisation easier an alternative strategy was attempted. Recent unpublished work in the

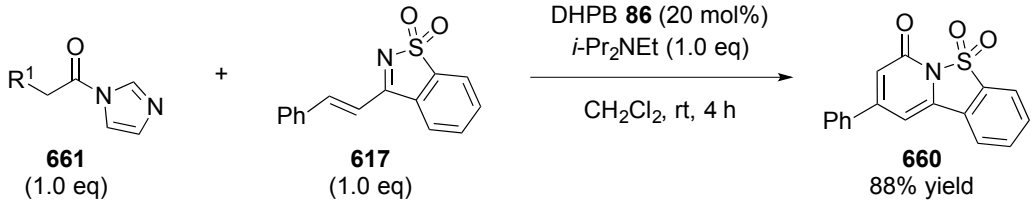
Smith group has shown that acyl imidazole reagents can act as suitable ammonium enolate precursors when applied in isothiourea catalysis. We proposed that using the acyl imidazoles in catalysis, followed by a mildly acidic work-up would remove any unreacted acyl imidazole, additional base and the Lewis base catalyst allowing purification by recrystallisation. Acyl imidazole **661** was prepared from the corresponding (phenylthio)acetic acid **84** and carbonyldiimazole (CDI) in quantitative yield. **661** was used immediately due to instability (Scheme 126).



84 (1.0 eq) → **661** Quant.

Scheme 126 - Synthesis of acyl imidazole 661.

Pleasingly, the reaction of **661** with **617** in the presence of DHPB **86** (20 mol%) and *i*-Pr_2NEt gave full conversion into **660** with an acidic work-up and recrystallisation from Et_2O giving the desired product in excellent 88% yield (Scheme 127). The reaction was also tried without the inclusion of any *i*-Pr_2NEt as it is proposed that the imidazole eliminated during the reaction may act as a suitable base for the deprotonation to the enolate. In this case, conversion was observed however, the reaction proceeded slowly with decomposition of Michael acceptor **617** and product **660** found after 24 h. Therefore, additional base is required to enhance the rate of reaction and minimise decomposition of materials.



661 (1.0 eq) + **617** (1.0 eq) → **660** 88% yield

Scheme 127 - Synthesis of 660 using acyl imidazoles as enolate precursors.

7.5 Conclusion

An enantioselective isothiourea-catalysed Michael addition-lactamisation process applying cyclic sulfonyl imines derived from cheap, commercially available saccharin and acetic acids has been established. A range of aryl acetic acid derivatives have been assessed in the methodology giving sultam products with variating substituents present at the C(8) position in typically excellent diastereo- and enantioselectivity. Under the limitations of this project a full study of the reaction scope, product utility and mechanism was not completed. Future work will look to explore this process fully.

7.6 References and Notes

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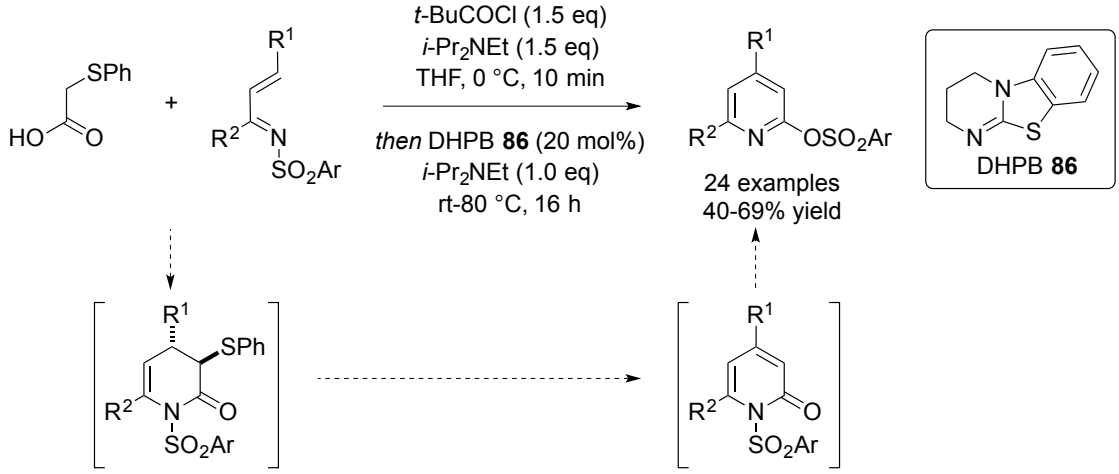
Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 8: Conclusions and Outlook

Chapter 8: Conclusions and Outlook

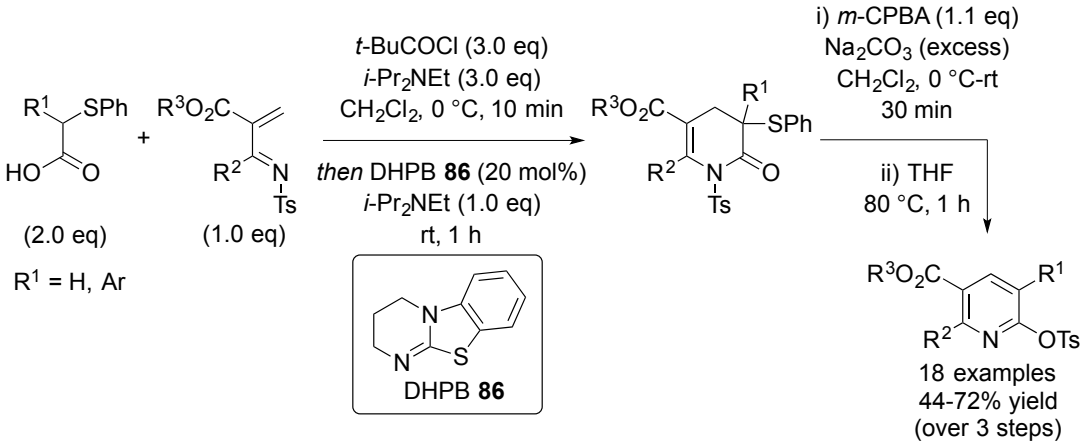
This thesis has described investigations into novel, state-of-the-art methodologies for the synthesis of functionalised heterocycles through the use of isothiourea C1-ammonium enolate catalysis.

Firstly, the DHPB-mediated synthesis of 2,4-substitued pyridine 6-sulfonates has been conveyed. This methodology applies (phenylthio)acetic acid and α,β-unsaturated ketimines in a one-pot Michael addition-lactamisation/PhSH elimination/*N*- to *O*-sulfonyl transfer cascade giving the pyridine sulfonates in moderate to good yield (40-69%) (Scheme 128). This reaction incorporates the *N*-sulfonyl group from the ketimine substrate into the synthetically valuable sulfonate functional handle with the utility of this group being demonstrated. This procedure proves scalable and can be conducted in open flask and bench grade solvent conditions. Moreover, this report remains one of the earliest organocatalytic methods for the preparation of pyridine compounds in a literature area dominated by catalytic organometallic methodologies.



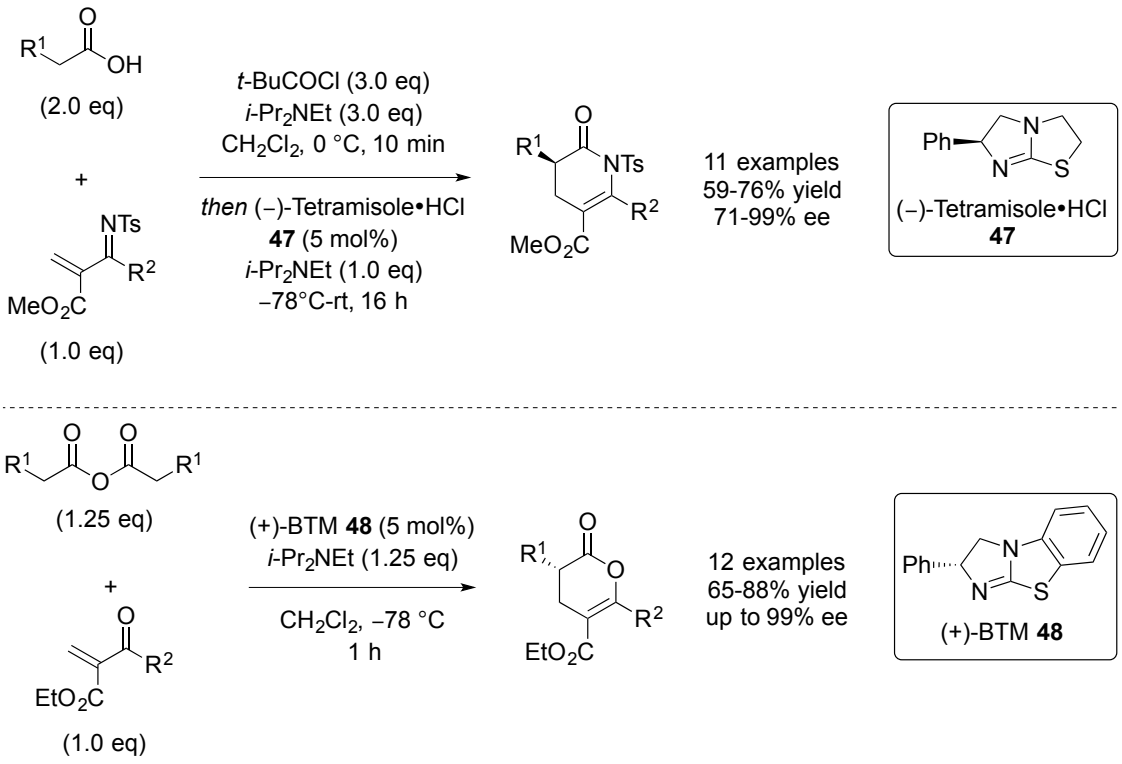
Scheme 128 - One-pot isothiourea-mediated synthesis of pyridines.

Following the initial report on the synthesis of pyridines, the subsequent studies focused on expanding the pyridine substituent classes available through isothiourea-mediated processes. Using (phenylthio)acetic acids and 2-*N*-tosyliminoacrylates a range of pyridine products were provided through a three-stage Michael addition-lactamisation, *S*-oxidation-sulfoxide elimination and *N*- to *O*-sulfonyl transfer protocol (Scheme 129). Overall, yields were moderate to good (44-72%) over the three-stage process giving 2,3- and 2,3,5-substituted pyridine 6-tosylates. The functionalisation of the installed sulfonate group allowed access into further substituent patterns such as 2,3-, 2,3,5-, 2,3,6 and 2,3,5,6-substituted pyridines



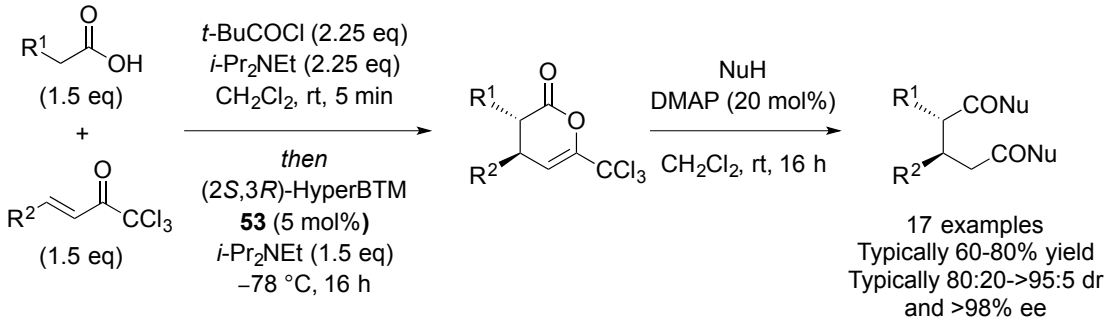
Scheme 129 - Three-stage synthesis of pyridines.

The 2-*N*-tosyliminoacrylates substrates were next applied alongside aryl acetic acids in an enantioselective isothiourea-catalysed methodology to give dihydropyridinones with typically excellent enantiocontrol (typically >90% ee) (Scheme 130). The structurally related 2-aroyl acrylate Michael acceptors were also probed in an isothiourea-catalysed Michael addition-cyclisation process. These substrates were discovered to possess high levels of reactivity and when used with carboxylic acids as the enolate precursor were found to susceptible to a racemic base-mediated background reaction. Optimisation studies led to the breakthrough of using homoanhydrides as the enolate precursor with less base required in the reaction and the desired dihydropyranones obtained in good to excellent enantioselectivity (up to 99% ee). The substituent pattern of these acrylate-based Michael acceptors had not been explored previously in enantioselective isothiourea-catalysed (or related) processes and thus provides a highly efficient route into novel classes of dihydropyridinones and dihydropyranones.



Scheme 130 - Application of 2-*N*-tosyliminoacrylates and 2-aroyl acrylates in enantioselective isothiourea-catalysis.

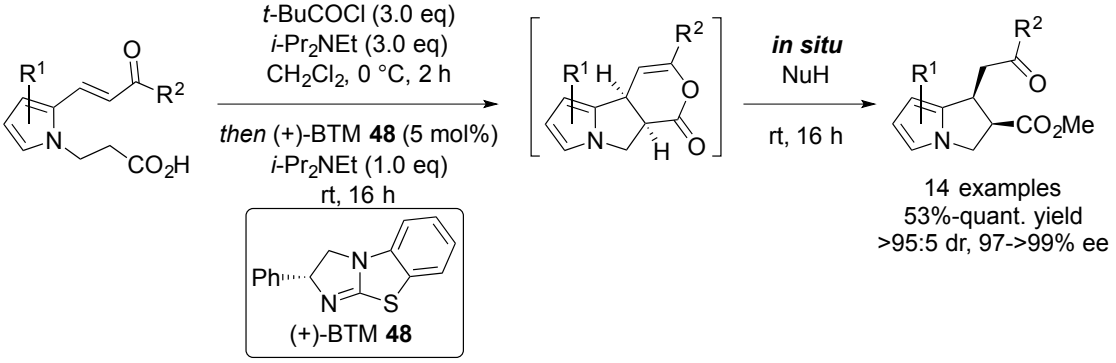
It was also shown that an enantioselective Michael addition-lactonisation of 2-aryl and 2-alkenylacetic acids with α,β-unsaturated trichloromethyl ketones, catalysed by (2*S*,3*R*)-HyperBTM was shown to give dihydropyranones with subsequent ring opening and substitution of the CCl_3 group providies a range of chiral diesters and diamides in high diastereo- and enantioselectivity (up to 95:5 and up to >99% ee) (Scheme 131). The use of trichloromethyl ketones as ester surrogates was found to offer a number of inherent advantages over the previously explored keto phosphonate substrates, most notably with improved bench stability and handling as well as a broader scope available.



Scheme 131 - Application of α,β-unsaturated trichloromethyl ketones in isothiourea-catalysis.

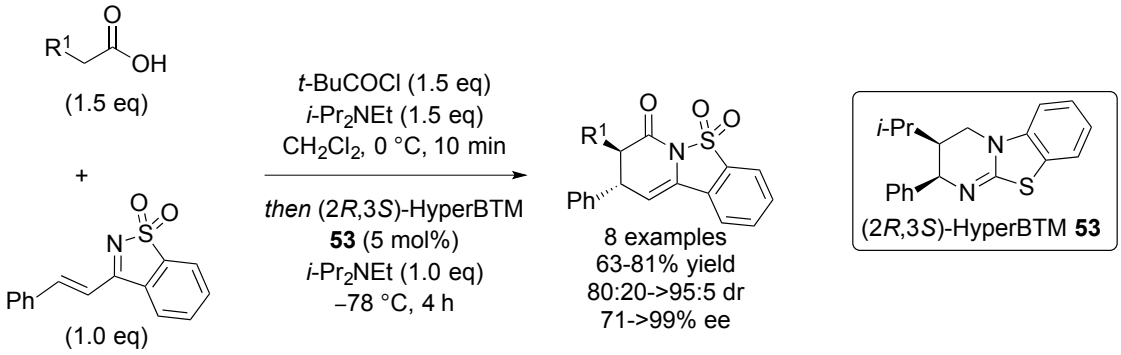
Efforts to access molecules with high importance and biological relevance led to the design and development of an enantioselective synthesis of chiral pyrrolizines (Scheme 132). Subjection of prepared pyrrolyl enone-acids to an isothiourea-catalysed Michael addition-

lactonisation/ring opening protocol gave the corresponding pyrrolizines with outstanding stereoselectivity (typically >95:5 dr and >99% ee). A wide range of nucleophiles were explored for the ring opening and thus deliver a variety of pyrrolizine amides and esters. The synthetic route for the preparation of the required pyrrolyl enone-acids was optimised to enable this methodology be efficient and reproducible. Computational studies were also conducted and provide valuable insight into the origins of the high levels of *syn*-selectivity.



Scheme 132 - Enantioselective synthesis of pyrrolizines.

Finally, a new project aiming to investigate the application of saccharin-derived Michael acceptors in isothiourea-catalysis has been initiated with the synthesis of a range of 8,9-dihydro-7*H* benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxides in good to excellent stereoselectivity (80:20->95:5 dr and 71->99% ee) (Scheme 133). Furthermore, these Michael acceptors can be utilised with 1-(1*H*-imidazol-1-yl)-2-(phenylthio)ethan-1-one in a Michael addition-lactamisation/PhSH elimination process giving access to the corresponding 1,2-benzoisothiazole pyridone-1,1-dioxide heterocycle in a chromatography-free procedure.



Scheme 133 - Application of saccharin-derived Michael acceptors in isothiourea-catalysis.

At the beginning of this PhD in late 2012, isothioureas had only just been discovered as powerful organocatalysts in C1-ammonium enolate catalysis. The work outlined in this thesis has continued the exploration and advancement within isothiourea-generated enolate intermediates and through a variety of Michael addition-cyclisation processes has provided access to a wide range of heterocycles and functional synthetic building blocks. Most notably,

the first examples within this area for the preparation of aromatic heterocycles has been developed. It can be envisioned that such formal cycloaddition processes could be further expanded in the area of heterocycle synthesis through the use of unexplored substrates in not only formal [4+2] cycloadditions but in broader formal cycloaddition processes. Furthermore, such formal cycloaddition processes may not be confined to the ammonium enolate reactivity mode, with a number of potential heteroyclic products possible through the use of isothiourea-generated acyl ammonium species. A defining feature of the reactions described in this thesis utilise a cyclisation step through a heteroatom to enable catalyst turnover. Therefore, a protocol that includes an external turnover mechanism has the potential to investigate a plethora of previously unexplored substrates. Moreover, in the general context of broadening isothiourea-catalysis, such an external turnover feature may allow the enantioselective synthesis of acyclic compounds. Subsequent endeavors within this area will aim to probe these ideas and assess the scope and limitations of isothiourea-catalysis.

Isothiourea-Mediated Synthesis of Functionalised Heterocycles

Chapter 9: Experimental

Chapter 9: Experimental

9.1 General Information

Reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum. For moisture sensitive reactions, solvents (THF, CH_2Cl_2, toluene, hexane and Et_2O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and CO_2(s)/acetone baths respectively. Temperatures of 0 °C to -50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. *Under reduced pressure* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica). Plates were visualised under UV light (254 nm) or by staining with either phosphomolybdic acid or $KMnO_4$ followed by heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated under a positive pressure of compressed air or on a Biotage® IsoleraTM 4, using Biotage® Snap Ultra or Biotage® KP Sil columns under the solvent system stated.

^1H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, ^1H, 75 MHz ^{13}C, 282 MHz ^{19}F), Bruker Avance II 400 (400 MHz, ^1H, 100 MHz ^{13}C, 376 MHz ^{19}F) or a Bruker Avance II 400 (500 MHz, ^1H, 125 MHz ^{13}C, 470 MHz ^{19}F) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to TMS = 0 as the internal standard for ^1H and ^{13}C NMR and relative to $CFCl_3$ = 0 for ^{19}F NMR. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), ABq (AB quartet), sept (septet), oct (octet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets, dt (doublet of triplets), dq (doublet of quartets) and td (triplet of doublets). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, py to denote pyridyl and br to denote broad.

Infrared spectra (ν_{max}/cm^{-1}) were recorded on either a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates or KBr discs or a Shimadzu IRAffinity-1

using a Pike attenuated total reflectance (ATR) accessory. Only the characteristic peaks are quoted.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. *Decomp* refers to decomposition.

HPLC analyses were obtained on two separate machines; a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector while the temperature was assumed to be 20 °C; a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns. All chiral HPLC traces were compared to the authentic racemic spectrum prepared in analogous fashion.

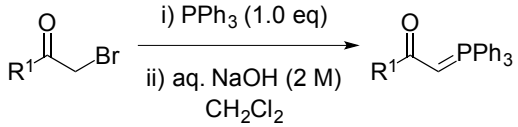
Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI), atmospheric solids analysis probe (ASAP) or nanospray ionisation (NSI) either at the University of St Andrews or the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution NSI MS was carried out on a Micromass Quattro II spectrometer and high resolution NSI MS on a Thermofisher LTQ Orbitrap XL spectrometer.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at rt.

9.2 Experimental for Chapter 2

9.2.1 General Experimental Procedures

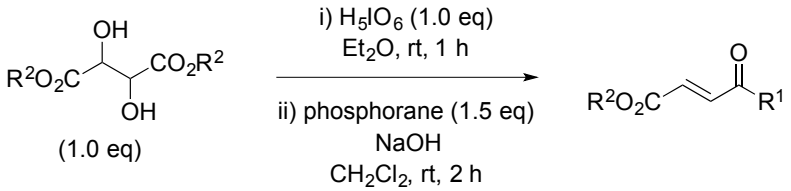
General Procedure A: *Preparation of phosphoranes*



To a solution of requisite bromide (1.0 eq) in CH_2Cl_2 (0.5 M) at rt was added triphenylphosphine (1 eq) and the solution was allowed to stir for 4 h before being concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2/H_2O (40:60) and aq. NaOH (2 M) was added. The reaction mixture was stirred at rt for 1 h before being extracted with CH_2Cl_2 (×3). The combined organic fraction were washed with brine, dried over $MgSO_4$, filtered and

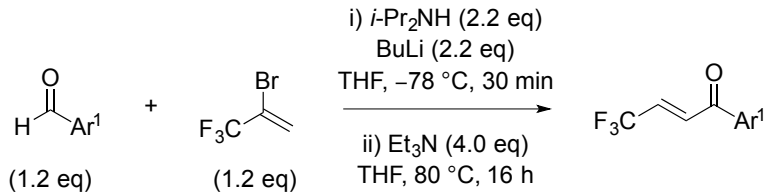
concentrated under reduced pressure to give the crude reaction mixture. Products were purified by recrystallisation or column chromatography in the solvent system stated.

General Procedure B*: Preparation of keto esters*



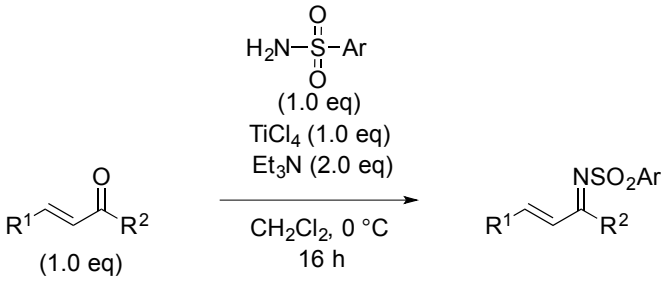
Keto esters prepared as per literature procedure.[72] To a solution of requisite tartrate (1.0 eq) in Et_2O (0.45 M) at rt was added periodic acid (1.0 eq) and the solution was allowed to stir for 1 h. The reaction mixture was filtered and the solids washed with THF. The organic fraction was dried over $MgSO_4$ and filtered. The requisite phosphorane (1.5 eq) was added and the reaction mixture was stirred at rt for 2 h before being concentrated under reduced pressure to give the crude reaction mixture. Products were purified by column chromatography in the solvent system stated.

General Procedure C*: Preparation of trifluoromethyl enones*



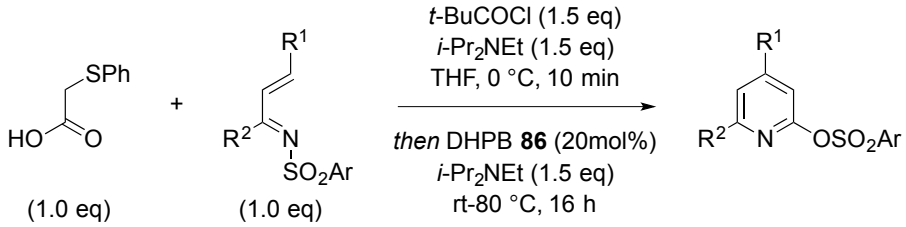
Trifluoromethyl enones prepared as per the literature procedure.[159] To a solution of *i*-Pr_2NH (2.2 eq) in THF at −78 °C was added *n*-BuLi (2.2 eq) and the solution was allowed to stir for 20 min. A pre-cooled (−78 °C) solution of 2-bromo-3,3,3-trifluoroprop-1-ene (1.0 eq) in THF was added dropwise at −78 °C followed by a further 5 min of stirring. The desired aldehyde (1.2 eq) was added dropwise followed by stirring at −78 °C for 30 min. The reaction mixture was quenched by addition of aq. HCl (1 M) and allowed to warm to rt. The reaction mixture was extracted with EtOAc (×3) and the combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude intermediate propargyl alcohol. The resulting residue was dissolved in THF before Et_3N (4.0 eq) was added and the reaction mixture was heated at 80 °C for 16 h. Once cool the reaction mixture was quenched by addition of aq. HCl (1 M) and the reaction mixture was extracted with EtOAc (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude reaction mixture. Products were purified by column chromatography in the solvent system stated.

General Procedure D*: Preparation of α,β-unsaturated ketimines*



To a solution of the requisite enone (1.0 eq) and requisite sulfonamide (1.0 eq) in CH_2Cl_2 (0.2 M) at 0 °C was added Et_3N (2.0 eq) followed by $TiCl_4$ (1.0 eq) and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was quenched by addition of H_2O and extracted with EtOAc (×3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude reaction mixture. Generally ketimines within the ester series proved troublesome to purify. These were judged to be >90% pure by ^1H NMR and suitable for use in this protocol. It should be noted that these issues were not encountered with ketimines from the trifluoromethyl series and these were recrystallised in the solvent system stated.

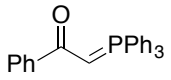
General Procedure E: *One-pot pyridine synthesis*



To a solution of (phenylthio)acetic acid (1.0 eq) in THF (0.06 M) were added *i*-Pr_2NEt (1.5 eq) and pivaloyl chloride (1.5 eq) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 10 min. The requisite Michael acceptor (1.0 eq), DHPB (20 mol%), and *i*-Pr_2NEt (1 eq) were then added at rt. The reaction mixture was stirred at rt until total consumption of the Michael acceptor as judged by TLC analysis. The reaction mixture was then heated at 80 °C for the required time for complete conversion to the pyridine. The reaction mixture was subsequently quenched by addition of H_2O and extracted with CH_2Cl_2 (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude reaction mixture. Products were purified by column chromatography in the solvent system stated.

9.2.2 Preparation of Phosphoranes

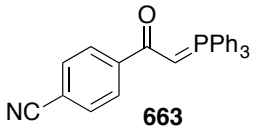
1-Phenyl-2-(triphenylphosphoranylidene)ethanone



662

Following general procedure A, 2-bromo-1-phenylethanone (10.0 g, 50.2 mmol) and triphenylphosphine (13.2 g, 50.2 mmol) in CH_2Cl_2 (100 mL) followed by aq. NaOH (2 M, 50 mL, 100 mmol) in CH_2Cl_2 (60 mL) and H_2O (90 mL) gave, after recrystallisation (EtOH:Et_2O), phosphorane as a white solid (13.0 g, 68%); mp 174-176 °C; {lit.[160] mp 173-175 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 4.46 (1H, d, *J* 24.5, C(2)*H*), 7.38-7.39 (3H, m, Ar*H* and Ar*H*), 7.48-7.52 (6H, m, Ar*H*), 7.57-7.60 (3H, m, Ar*H*), 7.73-7.77 (6H, m, 3 Ar*H*), 7.99-8.01 (2 H, m, Ar*H*). All data in accordance with literature.[160]

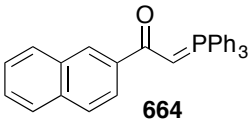
4-[2-(Triphenylphosphanylidene)acetyl]benzonitrile[161]



663

Following general procedure A, 2-(2-bromoacetyl)benzonitrile (5.00 g, 22.3 mmol) and triphenylphosphine (5.86 g, 22.3 mmol) in CH_2Cl_2 (50 mL) followed by aq. NaOH (2 M, 22 mL, 100 mmol) in CH_2Cl_2 (30 mL) and H_2O (45 mL) gave, after recrystallisation (EtOH:Et_2O), phosphorane as a white solid (7.30 g, 81%); mp 199-201 °C;[162] ^{1}H NMR (300 MHz, $CDCl_3$) 4.46 (1H, d, *J* 23.1, C(2)*H*), 7.46-7.52 (8H, m, Ar*H*), 7.59-7.73 (9H, m, Ar*H*), 8.02 (2H, d, *J* 8.42, C(1)Ar(2,6)*H*). All spectroscopic data in accordance with literature.[161]

1-(Naphthalene-2-yl)-2-(triphenylphosphanylidene)ethan-1-one

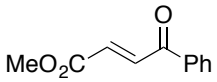


664

Following general procedure A, 2-(bromoacetyl)naphthalane (6.23 g, 25.0 mmol) and triphenylphosphine (6.57 g, 25.0 mmol) in CH_2Cl_2 (50 mL) followed by NaOH (2 M, 25 mL, 50.0 mmol) in CH_2Cl_2 (30 mL) and H_2O (45 mL) gave, after recrystallisation (EtOAc:Petrol), phosphorane as a white solid (8.71 g, 66%); mp 192-194 °C; {lit.[163] mp 190-192 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) 4.59 (1H, d, *J* 24.4, C(2)*H*), 7.42-7.58 (11H, m, Ar*H*), 7.68-7.82 (9H, m, Ar*H*), 8.07 (1H, dd, *J* 8.6, 1.7, Ar*H*), 8.49 (1 H, s, Ar*H*). All data in accordance with literature.[163]

9.2.3 Preparation of Keto-Esters

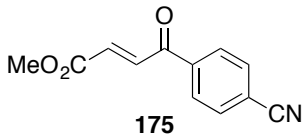
Methyl (2*E*)-4-oxo-4-phenylbut-2-enoate[72]



174

Following general procedure B, dimethyl tartrate (4.69 g, 26.3 mmol) and periodic acid (5.99 g, 26.3 mmol) in Et_2O (50 mL), phosphorane **662** (15.0 g, 39.4 mmol) in THF (60 mL) gave, after chromatographic purification (Et_2O:petrol 5:95), the title compound as a light yellow oil (4.8 g, 64%); ^{1}H NMR (500 MHz, $CDCl_3$) 3.82 (3H, s, OC*H*$_3$), 6.87 (1H, d, *J* 15.6, C(2)*H*), 7.47-7.50 (2H, m, Ar(3,5)*H*), 7.58-7.61 (1H, Ar(4)*H*), 7.90 (1H, d, *J* 15.6, C(3)*H*), 7.98 (2H, d, *J* 7.60, Ar(2,6)*H*).All data in accordance with literature.[72]

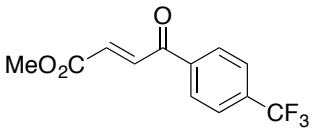
Methyl (2*E*)-4-(4-cyanophenyl)-4-oxobut-2-enoate



175

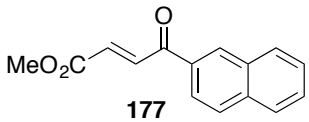
Following general procedure B, dimethyl tartrate (2.05 g, 11.5 mmol) and periodic acid (2.62 g, 11.5 mmol) in Et_2O (30 mL), phosphorane **663** (7.0 g, 17.3 mmol) in THF (35 mL) gave, after chromatographic purification (EtOAc:Petrol 30:70), the title compound as a light green solid (2.2 g, 59%); mp 168-170 °C; ν_{max} (ATR)/cm^{-1} 1629, 1668 (enone C=O), 1720 (ester C=O), 2231 (C-N), 3086 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.86 (3H, s, C*H*$_3$), 6.94 (1H, d, *J* 15.5, C(2)*H*), 7.83 (2H, *J* 8.5, Ar(3,5)*H*), 7.87 (1H, d, *J* 15.5, C(3)*H*), 8.08 (2H, d, *J* 8.5, Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 52.6 (*C*H$_3$), 117.1 (*C*N), 117.7 (Ar*C*(4)), 129.2 (Ar*C*(2,6)H), 132.8 (Ar*C*(3,5)), 133.6 (*C*(2)H), 135.3 (*C*(3)H), 139.5 (Ar*C*(1)), 165.6 (*C*(4)), 188.2 (*C*(1)); HRMS (NSI$^+$) $C_{12}H_{13}N_2O_3^+$ $[M+NH]^+$, requires 233.0921 found 233.0922 (+0.6 ppm).

Methyl (2*E*)-4-oxo-4-[4-(trifluoromethyl)phenyl]but-2-enoate[164]



Following general procedure B, dimethyl tartrate (1.06 g, 5.95 mmol) and periodic acid (1.36 g, 5.95 mmol) in Et_2O (20 mL), phosphorane **664** (4.0 g, 8.92 mmol) in THF (25 mL) gave, after chromatographic purification (EtOAc:Petrol 15:85), the title compound as a light yellow solid (2.12 g, 90%); mp 74-75 °C {lit.[164] 73.5-74.0 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) 3.86 (3H, s, C*H*$_3$), 6.92 (1H, d, *J* 15.6, C(3)*H*), 7.78 (2H, Ar(3)*H*), 7.89 (1H, d, *J* 15.6, C(2)*H*), 8.10 (2H, d, *J* 8.8, Ar(2)*H*). All data in accordance with literature.[164]

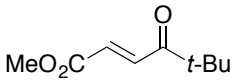
Methyl (2*E*)-4-(naphthalene-2-yl)-4-oxobut-2-enoate



177

Following general procedure B, dimethyl tartrate (2.21 g, 12.4 mmol) and periodic acid (2.83 g, 12.4 mmol) in Et_2O (30 mL), phosphorane **664** (8.0 g, 18.6 mmol) in THF (35 mL) gave, after chromatographic purification (EtOAc:Petrol 15:85), the title compound as a light yellow solid (3.60 g, 81%); mp 113-115 °C; ν_{max} (ATR)/cm^{-1} 1624, 1666 (enone C=O), 1724 (ester C=O), 2956, 3067 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 3.88 (3H, s, OC*H*$_3$), 6.97 (1H, d, *J* 15.5, C(2)*H*), 7.62 (2H, ddd, *J* 10.1, 7.8, 1.31, Np*H*), 7.89-8.06 (4H, m, Np*H*), 8.11 (1H, d, *J* 15.5, C(3)*H*), 8.53 (1H, s, Np(1)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 52.4 (*C*H$_3$), 124.0 (Np*C*H), 127.1 (Np*C*H), 127.9 (Np*C*H), 129.0 (Np*C*H), 129.1 (Np*C*H), 129.8 (Np*C*H), 131.2 (Np*C*H), 132.0 (*C*(2)H), 132.4 (Np*C*), 134.0 (Np*C*), 135.9 (Np*C*), 136.6 (*C*(3)H), 166.2 (*C*(1)), 189.1 (*C*(4)). HRMS (NSI^+) $C_{15}H_{13}O_3$ $[M+H]^+$, requires 241.0859 found 241.0860 (+0.3 ppm).

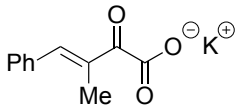
Methyl (2*E*)-5,5-dimethyl-4-oxohex-2-enoate



178

Following general procedure B, dimethyl tartrate (825 mg, 4.63 mmol) and periodic acid (1.06 g, 4.63 mmol) in Et_2O (20 mL), 3,3-dimethyl-1-(triphenylphosphanylidene)butan-2-one[160] (2.5 g, 6.94 mmol) in THF (25 mL) gave, after chromatographic purification (EtOAc:Petrol 5:95), the title compound as a light yellow oil (1.0 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) 1.13 (9H, s, (C*H*$_3$)$_3$), 3.74 (3H, s, C*H*$_3$), 6.71 (1H, d, *J* 15.5, C(3)*H*), 7.46 (1H, d, *J* 15.5, C(2)*H*). All data in accordance with literature.[165]

Potassium (*E*)-3-methyl-2-oxo-4-phenylbut-3-enoate

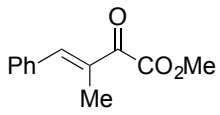


187

To a solution of benzaldehyde (2.55 mL, 25.0 mmol) and 2-ketobutyric acid (2.55 g, 25.0 mmol) in MeOH (4 mL) at 0 °C was added a solution of KOH (2.10 g, 37.5 mmol) in MeOH (15 mL) dropwise over 30 min. The reaction was heated to 40 °C for 1 h before being cooled and stirreed at 0 °C for 16 h. The precipitate was collected by filtration, washed with cold MeOH (×2), Et_2O and dried under vacuum to provide the title compound (3.76 g, 66%); mp 312

°C {lit.[166] 319 °C}; ^{1}H NMR (300 MHz, D_2O) 1.94 (3H, d, *J* 1.3, C*H*$_3$), 7.32-7.48 (6H, m, C(4)*H* and Ar*H*). All data in accordance with literature.[166]

Methyl (*E*)-3-methyl-2-oxo-4-phenylbut-3-enoate

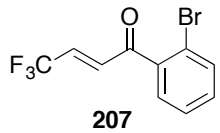


188

Acetyl chloride (13.6 mL, 190 mmol) was added to the MeOH (101 mL) at 0 °C before addition of **187** (3.76 g, 16.5 mmol) and reaction stirred for 30 min then warmed to rt over 2 h before heating at 65 °C for 16 h. The reaction was concentrated under reduced pressure with the resultant solid washed with H_2O and extracted with CH_2Cl_2 (×3). The combined organics were washed with sat. aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude reaction mixture. Chromatographic purification (EtOAc:Petrol 5:95) gave the title compound as light yellow oil (1.01 g, 30%); ^{1}H NMR (500 MHz, $CDCl_3$) 2.16 (3H, s, C(3)C*H*$_3$), 7.40-7.50 (6H, m, C(4)*H* and Ar*H*). All data in accordance with literature.[167]

9.2.4 Preparation of Trifluoromethyl Enones

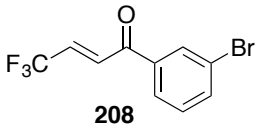
(2*E*)-1-(2-Bromophenyl)-4,4,4-trifluorobut-2-en-1-one



207

Following general procedure C, diisopropylamine (5.54 mL. 39.6 mmol) and *n*-BuLi (2.5 M in hexane, 15.8 mL, 39.6 mmol) in anhydrous THF (50 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (1.95 mL, 18.0 mmol) and 2-bromobenzaldehyde (2.52 mL, 21.6 mmol) gave intermediate propargyl alcohol. Subsequent treatment of crude with Et_3N (13.2 mL, 94.6 mmol) in THF (100 mL) gave after, chromatographic purification (EtOAc:Petrol 5:95), title compound as yellow oil (2.0 g, 40% over 2 steps); ν_{max} (ATR)/cm^{-1} 763 (CF_3), 1651, 1684 (C=O), 1125 (ArBr), 3063 (ArH); ^{1}H NMR (500 MHz, $CDCl_3$) 6.60 (1 H, dq, *J* 15.8, 6.6 C(3)*H*), 7.18 (2 H, dq, *J* 15.8, 2.0, C(2)*H*)), 7.37-7.46 (3 H, m, Ar*H*), 7.62 (1 H, m, Ar(2)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 119.8 (Ar*C*(2)Br) 122.5 (q, *J* 273.4, *C*F_3), 127.7 (Ar*C*H), 129.9 (Ar*C*H), 130.3 (q, *J* 35.5, *C*(3)H), 132.8 (Ar*C*H), 133.8 (Ar*C*H), 134.0 (q, *J* 5.5, *C*(2)H), 139.0 (Ar*C*(1)), 191.4 (*C*(1)O); δ_F (470 MHz, $CDCl_3$); -65.3 (C*F*$_3$); HRMS (APCI$^+$), $C_{10}H_7{}^{79}BrF_3O$ $[M+H]^+$, requires 278.9627 found 278.9627 (−0.3 ppm).

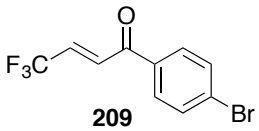
(2*E*)-1-(3-Bromophenyl)-4,4,4-trifluorobut-2-en-1-one



208

Following general procedure C, diisopropylamine (5.54 mL. 39.6 mmol) and *n*-BuLi (2.5 M in hexane, 15.8 mL, 39.6 mmol) in THF (50 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (1.95 mL, 18.0 mmol) and 3-bromobenzaldehyde (2.52 mL, 21.6 mmol) gave intermediate alcohol. Subsequent treatment with Et_3N (10.0 mL, 71.7 mmol) in THF (100 mL) gave, after chromatographic purification (EtOAc:Petrol; 5:95), the title compound as yellow solid (2.25 g, 45% over 2 steps); mp 30-32 °C; ν_{max} (ATR)/cm^{-1} 1125, 1651, 1686 (C=O), 3063 (ArH); ^{1}H NMR (500 MHz, $CDCl_3$) 6.83 (1 H, dq, *J* 15.5, 6.7 C(3)*H*), 7.41 (1 H, t, Ar(3)*H*), 7.48 (1 H, dq, *J* 15.5, 1.7 C(2)*H*), 7.75 (1 H, ddd, *J* 8.1, 2.1, 1.1, Ar(4)*H*), 7.88 (1 H, d, *J* 8.4, Ar(2)*H*), 8.09 (1 H, s, Ar(6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 122.3 (q, *J* 271.0, *C*F_3), 123.4 (Ar*C*(5)Br), 127.3 (Ar*C*(4)H), 130.4 (*C*(2)H), 130.5 (Ar*C*(3)H), 131 (q, *J* 35.9, *C*(3)H), 131.7 (Ar*C*(6)H), 136.9 (Ar*C*(2)H), 137.1 (Ar*C*(1)), 186.6 (*C*(1)). HRMS (NSI$^+$) $C_{10}H_{10}{}^{79}BrF_3NO$ $[M+NH_4]^+$ requires 295.9892 found 295.9897 (+1.6 ppm).

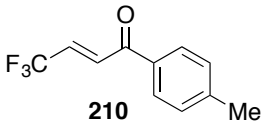
(*E*)-1-(4-Bromophenyl)-4,4,4-trifluorobut-2-en-1-one



209

Following general procedure C, diisopropylamine (7.71 mL, 55.0 mmol) and *n*-BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol) in THF (65 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (2.65 mL, 25.0 mmol) in THF (45 mL) and 4-bromobenzaldehyde (5.55 g, 30.0 mmol) gave the intermediate alcohol. Subseqent treatment with Et_3N (13.9 mL, 100 mmol) in THF (140 mL) gave, after chromatographic purification (Et_2O:petrol 3:97), the title compound as a light yellow solid (4.62 g, 66% over 2 steps); mp 52-54 °C; {lit.[159] mp 51-52 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.86 (1H, dq, *J* 15.5, 6.6, C(3)*H*), 7.51 (1H, dq, *J* 15.5, 2.0, C(2)*H*), 7.69-7.72 (2H, m, Ar(3,5)*H*), 7.86-7.88 (2 H, m, Ar(2,6)*H*). All data in accordance with literature.[159]

(2*E*)-4,4,4-Trifluoro-1-(4-methylphenyl)but-2-en-1-one

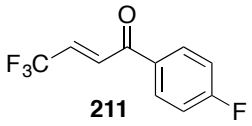


210

Following general procedure C, diisopropylamine (8.56 mL. 61.1 mmol) and *n*-BuLi (2.5 M in hexane, 24.4 mL, 61.1 mmol) in anhydrous THF (75 mL), 2-bromo-3,3,3-trifluoroprop-1-ene

(3.0 mL, 27.8 mmol) and 4-tolualdehyde (3.93 mL, 33.3 mmol) gave intermediate alcohol. Subsequent treatment with Et_3N (13.3 mL, 96 mmol) in THF (100 mL) gave, after chromatographic purification (EtOAc:Petrol 5:95) the title compound as yellow solid (2.85 g, 42% over 2 steps); mp 58-60 °C {lit.[168] 56-59 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 2.45 (3H, s, ArC*H*$_3$), 6.81 (1H, dq, *J* 15.6, 6.7 C(3)*H*), 7.32 (2H, d, Ar(3,5)*H*), 7.53 (1 H, dq, *J* 15.6, 2.1 C(2)*H*), 7.88 (2 H, d, *J* 8.30, Ar(2,6)*H*). All data in accordance with literature.[168]

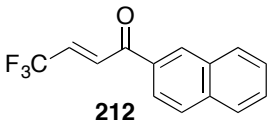
(2*E*)-4,4,4-Trifluoro-1-(4-fluorophenyl)but-2-en-1-one



211

Following general procedure C, diisopropylamine (12.17 mL. 88.7 mmol) and *n*-BuLi (2.5 M in hexane, 35.5 mL, 88.7 mmol) in THF (90 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (4.37 mL, 40.3 mmol) in THF (50 mL) and 4-fluorobenzaldehyde (5.19 mL, 48.3 mmol) gave intermediate alcohol. Subsequent treatment with Et_3N (26 mL, 187 mmol) in THF (250 mL) gave, after chromatographic purification (EtOAc:Petrol 5:95), the title compound as yellow solid (3.12 g, 35% over 2 steps); mp 78-80 °C; ν_{max} (ATR)/cm^{-1} 1151, 1564, 1597 (C=O), 3086 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 6.82 (1H, dq, *J* 15.5, 6.6 C(3)*H*), 7.20 (2H, t, Ar(3,5)*H*), 7.51 (1H, dq, *J* 15.5, C(2)*H*), 8.02 (2H, m, Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$); 116.2 (d, *J* 23.8, Ar*C*(3,5)H), 122.5 (q, *J* 272, *C*F$_3$) 130 (*C*(3)H), 130.3 (q, 35.6, *C*(2)H), 131.5 (d, *J* 9.92, Ar*C*(2,6)H), 132 (Ar*C*(1)), 166.4 (d, *J* 255.8, Ar*C*(4)F), 186.3 (*C*(1)); HRMS (APCI$^+$) $C_{10}H_7F_4O$ $[M+H]^+$, requires 219.0428 found 219.0427 (−0.2 ppm).

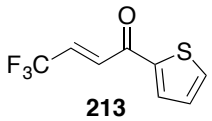
(2*E*)-4,4,4-Trifluoro-1-(naphthalene-2-yl)but-2-en-1-one



212

Following general procedure C, diisopropylamine (6.58 mL. 46.9 mmol) and *n*-BuLi (2.5 M in hexane, 18.8 mL, 46.9 mmol) in anhydrous THF (100 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (2.3 mL, 21.3 mmol) and 2-naphthaldehyde (4.0 g, 25.6 mmol) gave intermediate alcohol. Subsequent treatment with Et_3N (11.2 mL, 80.0 mmol) in THF (75 mL) gave, after chromatographic purification (EtOAc:Petrol 5:95), the title compound as yellow solid (2.94 g, 59% over 2 steps); mp 70-72 °C;[162] ^{1}H NMR (500 MHz, $CDCl_3$) 6.85 (1H, dq, *J* 15.5, 6.7 C(3)*H*), 7.55-7.69 (3H, m, Np*H*), 7.85-8.02 (4H, m, Np*H,* and C(2)*H*), 8.40 (1H, s, Np(2)*H*). All spectrascopic data in accordance with literature.[168]

(2*E*)-4,4,4-Trifluoro-1-(thiophen-2-yl)but-2-en-1-one

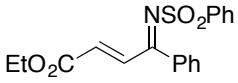


213

Following general procedure C, diisopropylamine (11.0 mL. 78.5 mmol) and *n*-BuLi (2.5 M in hexane, 31.4 mL, 78.5 mmol) in anhydrous THF (100 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (3.2 mL, 29.8 mmol) and 2-thiophene carboxaldehyde (3.27 mL, 35.7 mmol) gave intermediate alcohol. Subsequent treatment or crude with Et_3N (24.4 mL, 174.8 mmol) in THF (100 mL) gave, after chromatographic purification (EtOAc:Petrol 10:90), title compound as yellow solid (2.0 g, 27% over 2 steps); mp 47-49 °C;{lit.[168] 50-52 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.85 (1H, dq, *J* 15.4, 6.66 C(3)*H*), 7.21 (1H, dd, *J* 4.9, 3.9, thienyl(3)*H*), 7.40 (1H, dq, *J* 15.5, 2.0, C(2)*H*), 7.79 (1H, dd, *J* 5.0, 1.1, thienyl(2)*H*) 7.84 (1H, dd. *J* 3.9, 1.1, thienyl(4)*H*). All data in accordance with literature.[168]

9.2.5 Preparation of α,β-unsaturated ketimines

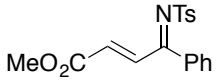
Ethyl (2*E*)-4-[(benzenesulfonyl)imino]-4-phenylbut-2-enoate



154

Following general procedure D, ethyl 3-benzoylacrylate (5.5mL, 30 mmol) and benzenesulfonamide (4.72 g, 30 mmol) were stirred in CH_2Cl_2 (50mL), Et_3N (8.3 mL, 60 mmol) and $TiCl_4$ (3.3 mL, 30 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as orange solid (4.59 g, 45%): mp 54-56 °C; {lit.[169] 51-53 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.1, CH_2CH_3), 4.33 (2H, q, *J* 7.0, CH_2CH_3), 6.27 (1H, d, *J* 16.2, C(3)*H*), 7.48 (1H, t, *J* 7.7, Ar*H*), 7.53-7.82 (8H, m, Ar*H*), 8.06 (1H, d, *J* 7.1, Ar*H*). All data in accordance with literature.[169]

Methyl (2*E*)-4-{[(4-methylbenzene)sulfonyl]imino}-4-phenylbut-2-enoate

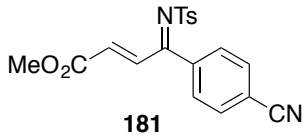


180

Following general procedure D, keto ester **174** (4.70 g, 24.7 mmol) and 4-toluenesulfonamide (4.23 g, 24.7 mmol) in CH_2Cl_2 (100 mL), Et_3N (6.79 mL, 49.4 mmol) and $TiCl_4$ (2.71 mL, 24.7 mmol) gave, after concentration under reduced pressure, crude ketimine **180** as a brown oil that was used crude without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) 2.42 (3 H, s,

SO_2ArCH_3), 3.82 (3 H, s, CH_3), 6.22 (1H, d, *J* 16.2, C(2)*H*), 7.24-7.57 (7H, m, Ar*H*), 7.89 (2H, d, *J* 7.46, SO_2Ar(2,6) *H*), 8.23 (1H, d, *J* 14.2, C(3)*H*).

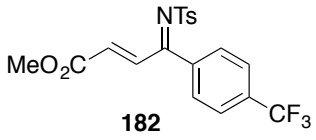
Methyl (2*E*)-4-(4-cyanophenyl)-4-{[(4-methylbenzene)sulfonyl]imino}but-2-enoate



181

Following general procedure D, keto ester **175** (2.00 g, 9.30 mmol) and 4-toluenesulfonamide (1.59 g, 9.30 mmol) in CH_2Cl_2 (25 mL), Et_3N (2.56 mL, 18.6 mmol) and $TiCl_4$ (1.02 mL, 9.30 mmol) gave, after concentration under reduced pressure, crude ketimine **181** as a brown oil that was used crude without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) 2.48 (3H, s, SO_2ArCH_3), 3.89 (3H, s, CH_3), 6.23 (1H, d, *J* 15.9, C(2)*H*), 7.38 (2H, d, *J* 7.92 SO_2Ar(3,5)*H*), 7.71-7.93 (4H, m, Ar*H*), 8.11 (2H, d, *J* 8.70, SO_2Ar(2,6)*H*), 8.29 (2H, d, *J* 15.6, C(3)*H*).

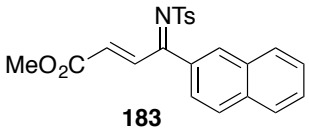
Methyl (2*E*)-4-{[(4-methylbenzene)sulfonyl]imino}-4-[4-(trifluoromethyl)phenyl]but-2-enoate



182

Following general procedure D, keto ester **176** (1.57 g, 6.08 mmol) and 4-toluenesulfonamide (1.04 g, 6.08 mmol) in CH_2Cl_2 (25 mL), Et_3N (1.68 mL, 12.2 mmol) and $TiCl_4$ (0.67 mL, 6.08 mmol) gave, after concentration under reduced pressure, crude ketimine **182** as a brown oil that was used crude without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.85 (3H, s, CH_3), 6.21 (1H, d, *J* 16.1, C(2)*H*), 7.35 (2H, d, *J* 7.8, SO_2Ar(3,5)*H*), 7.61-7.91 (6H, m, Ar*H*), 8.29 (1H, d, *J* 16.2, C(3)*H*).

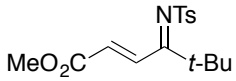
Methyl (2*E*)-4-{[(4-methylbenzene)sulfonyl]imino}-4-(naphthalene-2-yl)but-enoate



183

Following general procedure D, keto ester **177** (3.00 g, 12.5 mmol) and 4-toluenesulfonamide (2.15 g, 12.5 mmol) in CH_2Cl_2 (30 mL), Et_3N (3.44 mL, 25.0 mmol) and $TiCl_4$ (1.37 mL, 12.5 mmol) gave, after concentration under reduced pressure, crude ketimine **183** as a brown oil that was used crude without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) 2.48 (3H, s, SO_2ArCH_3), 3.87 (3H, s, CH_3), 6.29 (1H, d, *J* 16.3, C(2)*H*), 7.30-7.36 (3H, m, Ar*H*), 7.55-7.58 (4H, m, Ar*H*), 7.79-7.95 (5H, m, Ar*H* and C(3)*H*).

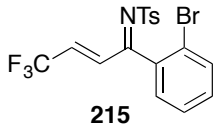
Methyl (2*E*)-5,5-dimethyl-4-{[(4-methylbenzene)sulfonyl]imino}hex-2-enoate



184

Following general procedure D, keto ester **178** (560 mg, 3.29 mmol) and 4-toluenesulfonamide (563 mg, 3.29 mmol) in CH_2Cl_2 (40 mL), Et_3N (0.91 mL, 6.58 mmol) and $TiCl_4$ (0.36 mL, 3.29 mmol) gave, after chromatographic purification (EtOAc:Petrol 30:70), the title compound as a brown solid (360 mg, 34%); mp 70-72 °C; ν_{max} (ATR)/cm^{-1} 1310 (S=O), 1597 (C=N), 2974 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 1.17 (9H, s, $(CH_3)_3$), 2.43 (3H, s, SO_2ArCH_3), 6.28 (1H, d, *J* 16.5, C(3)*H*), 7.31 (2H, d, *J* 8.2, $SO_2Ar(3,5)H$), 7.55 (1H, d, *J* 16.5, C(2)*H*), 7.82 (2H, d, *J* 8.2, $SO_2Ar(2,6)H$); ^{13}C NMR (125 MHz, $CDCl_3$) 21.6 (SO_2ArCH_3), 27.5 ($(CH_3)_3$), 42.5 ($C(CH_3)_3$, 52.3 (CH_3O), 126.7 (*C*(3)H), 127.3 ($SO_2ArC(2,6)H$), 129.4 ($SO_2ArC(3,5)H$), 137.9 ($SO_2ArC(4)$), 138.7 (*C*(2)H), 143.8 ($SO_2ArC(1)$), 165.0 (*C*(1)), 188.5 (CO_2Me); HRMS (APCI$^+$) $C_{16}H_{22}NO_4S$ $[M+H]^+$, requires 324.1264; found 324.1267 (+0.9 ppm).

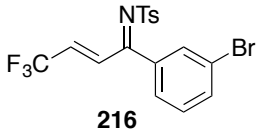
***N*-[(2*E*)-1-(2-bromophenyl)-4,4,4-trifluorobut-2-en-1-ylidene]-4-methylbenzene-1-sulfonamide**



215

Following general procedure D, and trifluoromethyl enone **207** (1.5 g, 5.37 mmol) and 4-toluenesulfonamide (0.92 g, 5.37 mmol) in CH_2Cl_2 (40 mL), Et_3N (1.50 mL, 10.7 mmol) and $TiCl_4$ (0.59 mL, 5.37 mmol) gave, after chromatographic purification (EtOAc:Petrol 20:80), the title compound as yellow oil (1.16 g, 50%); ν_{max} (ATR)/cm^{-1} 1100 (ArBr), 1287, 1314 (SO_2), 1558 (C=N), 297.2, 3072.6 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.41 (3H, s, SO_2ArCH_3), 6.00 (1H, dq, *J* 16.2, 6.4, C(3)*H*), 6.98 (1H, d, *J* 16.0, C(2)*H*), 7.26-7.35 (4H, m, Ar(3)*H*, Ar(5)*H* and $SO_2Ar(3,5)H$), 7.47 (1H, t, *J* 7.8, Ar(4)*H*), 7.61 (1H, dd, *J* 8.1, 2.3, Ar(6)*H*), 7.79 (2H, d, *J* 8.0, $SO_2Ar(2,6)H$); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (SO_2ArCH_3), 119.0 (Ar*C*(2)), 122.0 (q, *J* 266.8, CF_3), 127.5 (Ar*C*(4)H), 127.6 (Ar*C*(5)H), 127.9 ($SO_2ArC(2,6)H$), 129.7 ($SO_2ArC(3,5)H$), 131.8 (Ar*C*(3)H), 132.1 (*C*(3)H), 132.9 (Ar*C*(6)H), 134.7 ($SO_2ArC(4)$), 136.2 ($SO_2ArC(1)$), 137.6 (*C*(2)H), 144.8 (Ar*C*(1)), 172.6 (*C*(1)). HRMS (NSI$^+$) $C_{17}H_{14}{}^{79}BrF_3NO_2S^+$ $[M+H]^+$, requires 431.9875 found 431.9861 (−0.1 ppm).

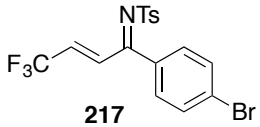
***N*-[(2*E*)-1-(3-Bromophenyl)-4,4,4-trifluoro-1-(4-methylphenyl)but-2-en-1-ylidene]benzene-1-sulfonamide**



216

Following general procedure D, and trifluoromethyl enone **208** (1.9 g, 6.8 mmol) and 4-toluenesulfonamide (1.16 g, 6.80 mmol) in CH_2Cl_2 (50 mL), Et_3N (1.88 mL, 13.6 mmol) and $TiCl_4$ (0.75 mL, 6.8 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as an orange solid (2.0 g, 80%): mp 64-66 ^oC; ν_{max} (ATR)/cm^{-1} 1100 (ArBr), 1287, 1314 (SO_2), 1558 (C=N), 297.2, 3072.6 (C-H); ^1H NMR (500 MHz, $CDCl_3$); 2.46 (3H, s, SO_2ArCH_3), 6.13 (1H, dq, *J* 16.3, 6.1, C(3)*H*), 7.30-7.37 (3H, m, Ar(5)*H* and SO_2Ar(3,5)*H*), 7.60 (1H, s, Ar(4)*H*), 7.70 (1H, d, *J* 7.8, C(2)*H*), 7.80-7.89 (4H, m, Ar(2)*H*, Ar(6)*H* and SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$); 21.7 (SO_2ArCH_3), 122.8 (Ar*C*(3)Br), 126.5 (SO_2ArC(2,6)H), 127.6 (Ar*C*(2)H), 128.8 (Ar*C*(4)H), 129.8 (Ar*C*(5)H and SO_2ArC(3,5)H), 130.3 (*C*(3)H), 131.2 (Ar*C*(4)H), 136.4 (*C*(2)H), 136.9 (SO_2ArC(4)), 144.6 (SO_2ArC(1) and *ArC*(1)), 171.2 (*C*(1)); HRMS (NSI^+) $C_{17}H_{14}{}^{79}BrF_3NO_2S^+$ $[M+H]^+$, requires 431.9875 found 431.9871 (−0.1 ppm).

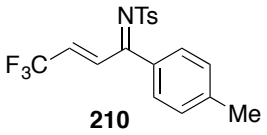
***N*-((*E*)-1-(4-Bromophenyl)-4,4,4-trifluorobut-2-en-1-ylidine)-4 methylbenzenesulfonamide**



217

Following general procedure D, trifluoromethyl enone **209** (4.62 g, 16.6 mmol) and 4-toluenesulfonamide (2.83 g, 16.6 mmol) in CH_2Cl_2 (70 mL), Et_3N (4.63 mL, 33.1 mmol) and $TiCl_4$ (1.82 mL, 16.6 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as a white solid (4.62 g, 65%); mp 78-80 °C; ν_{max} (ATR)/cm^{-1} 1304, 1549, 1574 (S=O), 1140 (S=O), 3103 (C-H); ^1H NMR (500 MHz, $CDCl_3$) 2.47 (3 H, s, CH_3), 6.15 (1 H, dq, *J* 16.3, 6.1, C(3)*H*), 7.38 (2 H, d, *J* 8.0, C(1)Ar(3,5)*H*), 7.62 (4 H, s, SO_2ArH), 7.85-7.92 (3 H, m, C(2)*H* and C(1)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (CH_3), 121.8 (q, *J* 282, CF_3), 126.4 (*C*(3)), 127.5 (C(1)Ar*C*(3,5)), 129.2 (C(1)Ar*C*(4)), 129.7 (C(1)A*rC*(2,6)), 131.5 (SO_2ArC), 131.5 (SO_2ArC), 132.2 (*C*(2)), 134.3 (SO_2ArC(4)), 137.1 (C(1)Ar*C*(1)), 144.5 (SO_2ArC(1)), 171.7 (*C*(1)); HRMS ($APCI^+$) $C_{17}H_{14}{}^{79}BrF_3NO_2S^+$ $[M+H]^+$, requires 431.9875; found 431.9875 (+0.0 ppm).

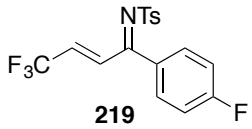
4-Methyl-*N*-[(2*E*)-4,4,4-trifluoro-1-(4-methylphenyl)but-2-en-1-ylidene]benzene-1-sulfonamide



210

Following general procedure D, trifluoromethyl enone **210** (2.0 g, 9.89 mmol) and 4-toluenesulfonamide (1.69 g, 9.89 mmol) in CH_2Cl_2 (50 mL), Et_3N (2.72 mL, 19.8 mmol) and $TiCl_4$ (1.10 mL, 9.89 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as an orange solid (2.8 g, 70%): mp 106-109 °C; ν_{max} (ATR)/cm^{-1} 1285 (SO_2), 1557 (C=N), 3261 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$); 2.42 (3H, s, ArC*H*$_3$), 2.45 (3H, s, SO_2ArC*H*$_3$), 6.11 (1H, dq, *J* 16.3, 6.12, C(3)*H*); 7.25 (2H, d, *J* 8.0, Ar(3)*H*), 7.34 (2H, d, *J* 8.1, SO_2Ar (3,5)*H*), 7.62 (3H, br s, Ar(2,6)*H*), 7.75-7.95 (3H, m, C(2)*H* and SO_2Ar (2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 (*C*H$_3$), 21.7 (SO_2Ar*C*H$_3$), 121.9 (q, *J* 265, *C*F$_3$), 127.4 (SO_2Ar*C*(2,6)H)), 129.6 (*C*(3)H, Ar*C*(3,5)H and SO_2Ar*C*(3,5)H), 130.3 (*C*(2)H), 131.9 (Ar*C*(2,6)H), 137.6 (Ar*C*(4) and SO_2Ar*C*(4)), 144.2 (Ar*C*(1) and SO_2Ar*C*(1)), 172.2 (*C*(1)); HRMS (NSI$^+$) $C_{18}H_{17}F_3NO_2S$ [M+H]$^+$, requires 368.0927 found 368.0928 (+0.4 ppm).

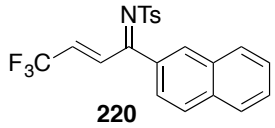
4-Methyl-*N*-[(2*E*)-4,4,4-trifluoro-1-(4-fluorophenyl)but-2-en-1-ylidene] benzene-1-sulfonamide



219

Following general procedure D, trifluoromethyl enone **211** (2.6 g, 11.9 mmol) and 4-toluenesulfonamide (2.03 g, 11.9 mmol) in CH_2Cl_2 (40 mL), Et_3N (3.28 mL, 23.8 mmol), $TiCl_4$ (1.31 mL, 11.9 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as an off-white solid (2.73 g, 62%): mp 78-80 °C; ν_{max} (ATR)/cm^{-1} 1303 (SO_2), 1564 (C=N), 3100 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3 H, s, SO_2ArC*H*$_3$), 6.12 (1 H, dq, *J* 16.3, 6.1, C(3)*H*), 7.15 (2 H, t, *J* 8.6, Ar(3,5)*H*), 7.36 (2 H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.77-7.84 (3 H, m, Ar(2)*H* and C(2)*H*), 7.89 (2 H, d, *J* 8.6, SO_2Ar(2,5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (SO_2Ar*C*H$_3$), 116.2 (d, *J* 22.2, Ar*C*(3,5)H), 121.7 (q, *J* 270.9, *C*F$_3$), 126.4 (Ar*C*(2,6)H), 127.5 (SO_2Ar*C*(2,6)H), 129.7 (SO_2Ar*C*(3,5)H and *C*(3)H), 132.8 (*C*(2)H), 137.2 (SO_2Ar*C*(4)), 139.3 (Ar*C*(1)), 144.4 (SO_2Ar*C*(1)), 165.2 (*C*(1)), 169.2 (d, *J* 519, Ar*C*(4)F); HRMS (APCI$^+$) $C_{17}H_{13}F_4NO_2S$ [M+H]$^+$, requires 372.0676 found 372.0677 (+0.3 ppm).

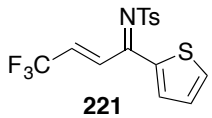
4-Methyl-*N*-[(1*E*)-4,4,4-trifluoro-1-(naphthalene-2-yl)but-2-en-1-ylidene]benzene-1-sulfonamide



220

Following general procedure D, trifluoromethyl enone **212** (2.00 g, 8.00 mmol) amd 4-toluenesulfonamide (1.37 g, 8.00 mmol) in CH_2Cl_2 (50 mL), Et_3N (2.20 mL, 16.0 mmol) and $TiCl_4$ (0.88 mL, 8.00 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as yellow solid (1.97 g, 61%): mp 120-122 °C; ν_{max} (ATR)/cm^{-1} 1287, 1288 (SO_2), 1550 (C=N), 3067 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.46 (3 H, s, SO_2ArCH_3), 6.18 (1 H, dq, *J* 16.3, 6.1, C(3)*H*), 7.37 (2 H, d, *J* 7.1, $SO_2Ar(3,5)H$), 7.58-7.65 (2 H, m, Ar*H*), 7.80-8.00 (7 H, m, Ar*H* and $SO_2Ar(2,6)H$), 8.20 (C(2)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (SO_2ArCH_3), 121.9 (q, *J* 271, CF_3), 124.9 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (Ar*C*H and Ar*C*H), 127.9 (Ar*C*H), 128.9 (*C*(3)H), 129.2 (Ar*C*H), 129.6 ($SO_2ArC(2,6)H$), 129.7 ($SO_2ArC(3,5)H$ and Ar*C*H), 132.3 (Ar*C* and Ar*C*), 137.5 ($SO_2ArC(4)$), 144.3 ($SO_2ArC(1)$ and Ar*C*(2)) 161.2 (*C*(1)); HRMS (NSI$^+$) $C_{21}H_{17}F_3NO_2S$ $[M+H]^+$, requires 404.0927 found 404.0924 (−0.6 ppm).

4-Methyl-*N*-[(2*E*)-4,4,4-trifluoro-1-(thiophen-2-yl)but-2-en-1-ylidene]benzene-1-sulfonamide

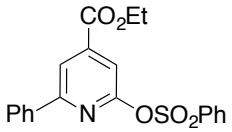


221

Following general procedure D, trifluoromethyl enone **213** (1.90 g, 6.80 mmol) and 4-toluenesulfonamide (1.16 g, 6.80 mmol) in CH_2Cl_2 (50 mL), Et_3N (1.88 mL, 13.6 mmol) and $TiCl_4$ (0.75 mL, 6.8 mmol) gave, after recrystallisation (Et_2O:Petrol), the title compound as an orange solid (2.0 g, 80%): mp 102-104 °C; ν_{max} (ATR)/cm^{-1} 1288 (S=O), 1533, 3086 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$); 2.45 (3H, s, SO_2ArCH_3), 6.12 (1H, dq, *J* 16.2, 6.0, C(3)*H*), 7.16 (1H, dd, *J* 5.02, 3.89, C(1)Ar(4)*H*), 7.35 (2H, d, *J* 8.1, $SO_2ArC(3,5)H$), 7.63 (1H, d, *J* 3.9, C(1)Ar(3)*H*), 7.70-7.75 (3H, m, C(1)Ar(5)*H* and C(2)*H*), 7.88 (2H, d, *J* 8.30, $SO_2ArC(2)H$); ^{13}C NMR (125 MHz, $CDCl_3$); 21.7 (SO_2ArCH_3), 121.7 (q, *J* 270, CF_3), 127.4 ($SO_2ArC(2,6)H$), 127.8 (*C*(3)H), 128.9 (C(1)Ar*C*(4)H), 129.6 ($SO_2ArC(3,5)H$), 131.6 (C(1)Ar*C*(5)H), 136.6 (C(1)Ar*C*(3)H), 136.9 (*C*(2)H), 137.3 ($SO_2ArC(4)$), 144.22 (C(1)Ar*C*(2) and $SO_2ArC(1)$), 165.6 (*C*(1)); HRMS (NSI$^+$) $C_{15}H_{13}F_3NO_2S_2$ $[M+H]^+$, requires 360.0334 found 360.0336 (0.5 ppm).

9.2.6 One-Pot Pyridine Synthesis

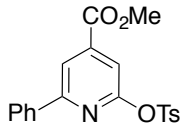
Ethyl 2-phenyl-6-((phenylsulfonyl)oxy)isonicotinate



156

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) in THF (6 mL), *i*-Pr_2NEt (157 μL, 0.9 mmol), pivaloyl chloride (110 μL, 0.9 mmol), ketimine **154** (206 mg, 0.6 mmol), DHPB **86** (22 mg, 0.12 mmol), and *i*-Pr_2NEt (101 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (EtOAc:Petrol 10:90), the title compound as a yellow solid (155 mg, 67%); mp 119-120 °C; ν_{max} (ATR)/cm^{-1} 1362, 1558 (S=O); 1724 (C=O); 2938, 2980 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 (3H, t, *J* 7.1, CH_2CH_3), 4.45 (2H, q, *J* 7.1 CH_2CH_3), 7.39-7.44 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.55-7.61 (3H, m, SO_2Ar(3,5)*H* and SO_2Ar(4)*H*), 7.68-7.77 (3H, m, py(3)*H*, Ar(2,6)*H*), 8.06-8.10 (2H, m, SO_2Ar(2,6)*H*), 8.21 (1H, d, *J* 1.06, py(5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 14.2 (CH_3), 62.3 (CH_2), 113.4 (py*C*(3)), 118.2 (py*C*(5)), 127.0 (py(6)Ar*C*(4)H), 128.8 (py(6)Ar*C*(2,6)H and py(6)Ar*C*(3,5)H), 129.1 (SO_2Ar*C*(2,6)H), 130.0 (SO_2Ar*C*(3,5)H), 134.1 (SO_2Ar*C*(4)H), 136.6 (SO_2Ar*C*(1)), 137.3 (py(6)Ar*C*(1)), 143.0 (py*C*(6)), 157.2 (py*C*(4)), 157.4 (py*C*(2)), 163.9 (*C*(1)); HRMS (NSI^+) $C_{20}H_{18}NO_5S^+$ $[M+H]^+$, requires 384.0900 found 384.0899 (−0.3 ppm).

Methyl 2-{[(4-methylbenzene)sulfonyl]oxy}-6-phenylpyridine-4-carboxylate

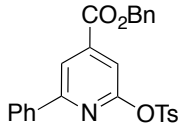


190

Following general procedure E, (phenylthio)acetic acid (4.41 g, 26.2 mmol) in THF (400 mL), *i*-Pr_2NEt (6.85 mL, 39.3 mmol), pivaloyl chloride (4.73 mL, 39.3 mmol), ketimine **154** (9.0 mg, 26.2 mmol), DHPB **86** (1.00 g, 5.24 mmol), and *i*-Pr_2NEt (4.57 mL, 26.2 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (EtOAc:Petrol 10:90), the title compound as a red solid (5.00 g, 50%); mp 118-120 °C; ν_{max} (ATR)/cm^{-1} 1169, 1364 (S=O), 1557, 1730 (C=O), 2953 (Ar-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.47 (3H, s, SO_2ArCH_3), 3.99 (3H, s, OCH_3), 7.36 (2H, d, *J* 8.04, SO_2Ar(3,5)*H*), 7.40-7.43 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.58 (1H, d, *J* 1.0, py(3)*H*), 7.76-7.78 (2H, m, Ar(2,6)*H*), 7.94 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.21 (1H, d, *J* 1.0, py(5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 53.1 (OCH_2), 113.5 (py*C*(3)), 118.1 (py*C*(5)), 127.0 (py(6)Ar*C*(2,6)H), 128.8 (SO_2Ar*C*(2,6)H), 129.7 (SO_2Ar*C*(3,5)H), (py(6)Ar*C*(3,5)H), 130.1 (py(6)Ar*C*(4)H), 134.1 (SO_2Ar*C*(4)), 136.6

($SO_2ArC(1)$), 142.5 (py(6)Ar*C*(1)), 145.3 (py*C*(6)), 157.2 (py*C*(4)), 157.6 (py*C*(2)), 164.5 (*C*(1)); HRMS (NSI^+) $C_{20}H_{18}NO_5S$ $[M+H]^+$, requires 384.0900 found 384.0901 (+0.2 ppm).

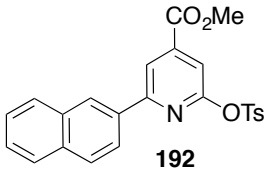
Benzyl 2-([(4-methylbenzene)sulfonyl]oxy)-6-phenylpyridine-4-carboxylate



191

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (157 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol), ketimine **154** (252 mg, 0.6 mmol) and *i*-Pr_2NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a white solid (166 mg, 60%); mp 64-66 °C; ν_{max} (ATR)/cm^{-1} 1168, 1362 (S=O), 1734 (C=O), 3068 (Ar-H); ^1H NMR (500 MHz, $CDCl_3$) 2.49 (3H, s, SO_2ArCH_3), 5.55 (2H, s, CO_2CH_2Ph), 7.35-7.48 (10H, m, Ar*H*), 7.58 (1H, s, pyC(3)*H*), 7.78 (2H, m, $SO_2ArC(3,5)H$), 7.96 (2H, d, *J* 8.4, py(6)Ar(2,6)*H*), 8.24 (1H, m, py(5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$); 21.8 (SO_2ArCH_3), 67.9 (CO_2CH_2Ph), 113.5 (py*C*(5)H), 118.2 (py*C*(3)H), 127.0 ($SO_2ArC(2,6)H$), 128.6 (C(1)Ar(2,6)H), 128.7-128.8 py(6)Ar*C*(4)H, py(6)Ar*C*(2,6)H and C(1)Ar(4)H), 129.7 (C(1)Ar*C*(3,5)H), 130.1 ($SO_2ArC(3,5)H$), 134.2 ($SO_2ArC(1)$), 135.0 (C(1)Ar*C*(1)), 136.6 ($SO_2ArC(4)$), 142.6 (py(6)Ar*C*(1)), 145.3 (py*C*(6)), 157.2 (py*C*(4)), 157.6 (py*C*(2)), 163.9 (*C*(1)); HRMS (NSI^+) $C_{26}H_{22}NO_5S$ $[M+H]^+$, requires 460.1213 found 460.1200 (−2.9 ppm).

Methyl 2-{[(4-methylbenzene)sulfonyl]oxy}-6-(naphthalene-2-yl)pyridine-4-carboxylate

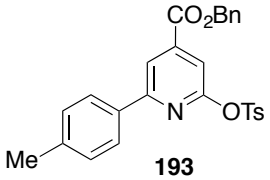


192

Following general procedure E, (phenylthio)acetic acid (427 mg, 2.54 mmol) and *i*-Pr_2NEt (0.66 mL, 3.81 mmol) in THF (40 mL) were added pivaloyl chloride (0.74 mL, 3.81 mmol) DHPB **86** (97 mg, 0.51 mmol), crude ketimine **183** (1.00 g, 2.54 mmol) and *i*-Pr_2NEt (0.44 mL, 2.54 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a green solid (760 mg, 69%); mp 142-144 °C; ν_{max} (ATR)/cm^{-1} 1171 (C-O), 1369 (SO_2), 1732 (C=O), 2951 (C-H) ^1H NMR (400 MHz, $CDCl_3$) 2.49 (3H, s, SO_2ArCH_3), 4.02 (3H, s, CO_2CH_3), 7.39 (2H, d, *J* 8.0, $SO_2Ar(3,5)H$), 7.52-7.56 (2H, m, Np*H*), 7.61 (1H, d, *J* 1.0, py(5)*H*), 7.85-7.87 (4H, m, Np*H*), 7.98 (2H, d, *J*

8.4, SO_2Ar(2,6)*H*), 8.26 (1H, s, py(3)*H*), 8.35 (1H, d, *J* 1.05, Np(1)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2Ar*C*H_3), 53.1 (O*C*H_3), 113.5 (py*C*(5)H), 118.4 (py*C*(3)H), 124.1 (Np*C*H), 126.6 (Np*C*H), 127.0 (Np*C*H), 127.2 (Np*C*H), 127.7 (Np*C*H), 128.5 (Np*C*H), 128.8 (Np*C*H), 128.9 (SO_2Ar*C*(2,6)H), 129.8 (SO_2Ar*C*(3,5)H), 133.2 (Np*C*(10)), 133.9 (Np*C*(5)), 134.1 (SO_2Ar*C*(1)), 134.3 (Np*C*(2)), 142.5 (SO_2Ar*C*(4)), 145.3 (py*C*(6)), 157.2 (py*C*(4)), 157.7 (py*C*(2)), 164.5 (*C*(1)); HRMS (NSI$^+$) $C_{24}H_{20}NO_5S$ $[M+H]^+$, requires 434.1057 found 434.1051 (−1.3 ppm).

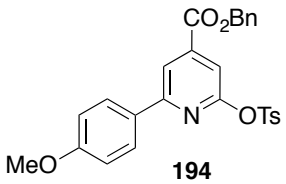
Benzyl 2-(4-methylphenyl)-6-([(4-methylbenzene)sulfonyl]oxy)pyridine-4-carboxylate



193

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (157 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol), benzyl (2*E*)-4-(4-tolyl)-4-(tosylimino)but-2-enoate (270 mg, 0.6 mmol) and *i*-Pr_2NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a white solid (166 mg, 60%); mp 127-130 °C; ν_{max} (ATR)/cm^{-1} 1171 (C-O), 1367 (SO_2), 1722 (C=O), 3088 (Ar-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.40 (3H, s, py(6)ArC*H*$_3$), 2.47 (3H, s, SO_2ArC*H*$_3$), 5.41 (2H, s, CO_2C*H*$_2$Ph), 7.21 (2H, d, *J* 8.7, py(6)Ar(3,5)*H*), 7.35-7.47 (7H, m, Ar*H*), 7.55 (1H, s, py(5)*H*), 7.66 (2H, d, *J* 7.6, SO_2ArC(2,6)*H*), 7.94 (2H, d, *J* 7.6, py(6)Ar(2,6)*H*) 8.19 (1H, s, py(3)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.4 (Ar*C*H_3), 21.7 (SO_2Ar*C*H_3), 67.9 (CO_2*C*H_2Ph), 113.0 (py*C*(5)H), 117.9 (py*C*(3)H), 126.9 (SO_2Ar*C*(2,6)H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (py(6)Ar*C*(2,6)H), 128.9 (Ar*C*H) 129.5 (py(6)*Ar*(3,5)H), 129.7 (Ar*C*H), 133.9 (SO_2*ArC*(1)), 134.2 (py(6)Ar*C*(4)), 135.0 (C(1)Ar*C*(1)), 140.4 (SO_2Ar*C*(4)), 142.4 (py(6)Ar*C*(1)), 145.2 (py*C*(6)), 157.3 (py*C*(4)), 157.4 (py*C*(2)), 163.9 (*C*(1)); HRMS (APCI$^+$) $C_{27}H_{24}NO_5S$ $[M+H]^+$, requires 474.1370 found 474.1369 (−0.1 ppm).

Benzyl 2-(4-methoxyphenyl)-6-([(4-methylbenzene)sulfonyl]oxy)pyridine-4-carboxylate

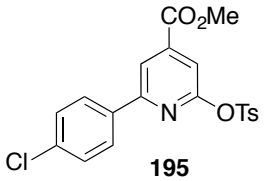


194

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (157 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22

mg, 0.12 mmol), benzyl (2*E*)-4-(4-methoxyphenyl)-4-(tosylimino)but-2-enoate (270 mg, 0.6 mmol) and *i*-Pr_2NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as an orange solid (150 mg, 51%); mp 129-131 °C; ν_{max} (ATR)/cm^{-1} 1165 (C-O), 1084, 1251 (ArOMe), 1552 (SO_2), 1726 (C=O), 2936, 2995 (Ar-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.46 (3H, s, OC*H*$_3$), 3.86 (3H, s, SO_2ArC*H*$_3$), 5.40 (2H, s, CO_2CH_2Ph), 6.90 (2H, d , *J* 8.72, py(6)Ar(3,5)*H*), 7.34-7.50 (8H, m, Ar*H*), 7.70 (2H, d, *J* 8.6, SO_2ArC(2,6)*H*), 7.93 (2H, d, *J* 8.4, py(6)Ar(2,6)*H*), 8.14 (1H, s, pyC(3)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2Ar*C*H_3), 55.4 (O*C*H_3), 67.9 (*C*H_2), 112.4 (py*C*(5)H), 114.1 (py*C*(3)H), 117.3 (py(6)Ar*C*(3)H), 128.5 (SO_2Ar*C*(2)H), 128.8 (C(1)Ar*C*(2,6)H), 128.8 (C(1)Ar*C*(3,5)H), 128.8 (C(1)Ar*C*(4)H), 128.8 (py(6)ArC(2)H), 129.3 (SO_2Ar*C*(1)), 129.7 (SO_2Ar*C*(3,5)H), 134.2 (py(6)Ar*C*(1)), 135.0 (C(1)Ar*C*(1)), 142.4 (SO_2Ar*C*(4)), 145.2 (py*C*(6)), 157.0 (py*C*(4)), 157.5 (py(6)Ar*C*(4)), 161.3 (py*C*(2)), 164.0 (*C*(1)); HRMS (APCI$^+$) $C_{27}H_{24}NO_6S$ $[M+H]^+$, requires 490.1319 found 490.1311 (−1.6 ppm).

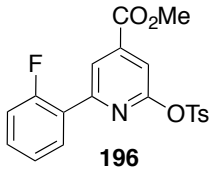
Methyl 2-(4-chlorophenyl)-6-([(4-methylbenzene)sulfonyl]oxy)pyridine-4-carboxylate



195

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (157 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol), methyl (2*E*)-4-(4-chlorophenyl)-4-(tosylimino)but-2-enoate (0.227 g, 0.6 mmol) and *i*-Pr_2NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a white solid (130 mg, 54%); mp 120-122 °C; ν_{max} (ATR)/cm^{-1} 1086 (ArC(4)) 1171, 1181 (SO_2), 1734 (C=O), 2956, 3096 (Ar-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.47 (3H, s, C*H*$_3$), 3.98 (3H, s, SO_2ArC*H*$_3$), 7.36-7.37 (4H, m, Ar(3,5)*H* and SO_2Ar(3,5)*H*), 7.57 (1H, s, py(3)*H*), 7.70 (2H, d, *J* 8.0, SO_2Ar(2,6)*H*), 7.92 (2H, *J* 7.7, Ar(2,6)*H*), 8.16 (1H, s, py(5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (*C*H_3), 53.1 (SO_2Ar*C*H_3), 113.7 (py*C*(5)H), 117.9 (py*C*(3)H), 128.3 (SO_2Ar*C*(2,6)H), 128.8 (py(6)Ar*C*(2,6)H), 129.0 (py(6)Ar*C*(3,5)H), 129.7 (SO_2Ar*C*(3,5)H), 134.1 (SO_2Ar*C*(1)), 135.1 (py(6)Ar*C*(4)Cl), 136.3 (py(6)Ar*C*(1)), 142.7 (SO_2Ar*C*(4)), 145.4 (py*C*(6)), 155.9 (py*C*(4)), 157.6 (py*C*(2)), 164.3 (*C*(1)); HRMS (APCI$^+$) $C_{20}H_{17}ClNO_5S$ $[M+H]^+$, requires 418.0510 found 418.0510 (−0.1 ppm).

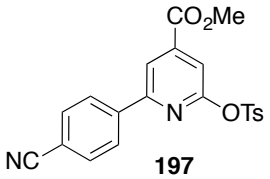
Methyl 2-(2-fluorophenyl)-6-{[(4-methylbenzene)sulfonyl]oxy}pyridine-4-carboxylate



196

Following general procedure E, (phenylthio)acetic acid (234 mg, 1.39 mmol) and *i*-Pr_2NEt (360 μL, 2.09 mmol) in THF (21 mL) were added pivaloyl chloride (260 μL, 2.09 mmol) DHPB **86** (53 mg, 0.28 mmol), methyl (2E,4Z)-4-(2-fluorophenyl)-4-(tosylimino)but-2-enoate (500 mg, 1.39 mmol) and *i*-Pr_2NEt (240 mL, 1.39 mmol for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a yellow solid (375 mg, 65%); mp 86-88 °C; ν_{max} (ATR)/cm^{-1}1368 (SO_2), 1735 (C=O), 2974 (C-H); ^1H NMR (500 MHz, $CDCl_3$) 2.46 (3H, s, SO_2ArCH_3), 3.98 (3H, s, OCH_3), 7.13-7.18 (2H, m, Ar(3)*H* and Ar(5)*H*), 7.35 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.37-7.42 (1H, m, Ar(4)*H*), 7.57-7.61 (2H, m, py(3)*H* and Ar(6)*H*), 7.93 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.31 (1H, s, py(5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 53.1 (OCH_3), 113.9 (py*C*(3)H), 116.4 (d, *J* 23.0, Ar*C*(3)H), 122.4 (d, *J* 12.3, py*C*(5)H), 124.4 (d, *J* 3.42, Ar*C*(5)H), 124.8 (d, *J* 10.6, Ar*C*(1)), 128.8 (SO_2Ar*C*(2,6)H), 129.7 (SO_2Ar*C*(3,5)H), 131.0 (d, *J* 1.96 (Ar*C*(6)H), 131.6 (d, *J* 8.74, Ar*C*(4)H), 134.0 (SO_2Ar*C*(4)), 142.4 (SO_2Ar*C*(1)), 145.4 (py*C*(6)), 153.0 (py*C*(4)), 157.4 (py*C*(2)), 160.7 (d, *J* 254, Ar*C*(2)), 164.4 (*C*(1)); ^{19}F NMR (470 MHz, $CDCl_3$); −115.4 (Ar*F*); HRMS (NSI^+) $C_{20}H_{17}FNO_5S$ $[M+H]^+$, requires 402.0806 found 402.0803 (−0.7 ppm).

Methyl 2-(4-cyanophenyl)-6-{[(4-methylbenzene)sulfonyl]oxy}pyridine-4-carboxylate

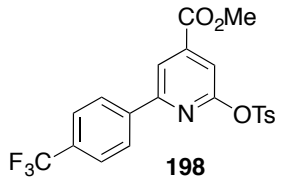


197

Following general procedure E, (phenylthio)acetic acid (456 mg, 2.71 mmol) and *i*-Pr_2NEt (0.71 mL, 4.10 mmol) in THF (40 mL) were added pivaloyl chloride (0.5 mL, 4.10 mmol) DHPB **86** (103 mg, 0.54 mmol), crude ketimine **181** (1.00 g, 2.71 mmol) and *i*-Pr_2NEt (0.47 mL, 2.71 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 20:80), the title compound as a brown solid (664 mg, 60 %); mp 154-156 °C; ν_{max} (ATR)/cm^{-1} 1165 (C-O), 1370 (SO_2), 1734 (C=O), 2224 (ArCN) ^1H NMR (400 MHz, $CDCl_3$) 2.49 (3H, s, SO_2ArCH_3), 4.00 (3H, s, CO_2CH_3), 7.38 (2H, d, *J* 8.56, SO_2Ar(3)*H*), 7.65 (1H, d, *J* 1.0, py(3)*H*), 7.71 (1H, d, *J* 8.0, Ar(2,6)*H*), 7.92 (4H, m, SO_2Ar(2,6)*H* and Ar(3,5)*H*), 8.24 (1H, d, *J* 1.0, py(5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 53.3 (OCH_3), 113.6 (Ar*C*(4)), 114.9 (py*C*(3)H), 118.4 (Ar(4)*C*N), 118.6 (py*C*(5)H), 127.5 (Ar*C*(2,6)H), 128.7 (SO_2Ar*C*(2,6)H), 129.8 (SO_2Ar*C*(3,5)H), 132.6 (Ar*C*(3,5)H), 134.0

($SO_2ArC(1)$), 140.7 ($SO_2ArC(4)$), 143.0 ($ArC(1)$), 145.6 (py$C(6)$), 154.9 (py$C(4)$), 157.8 (py$C(2)$), 164.0 ($C(1)$); HRMS (NSI^+) $C_{21}H_{17}N_2O_5S$ $[M+H]^+$, requires 409.0853 found 409.848 (−1.1 ppm).

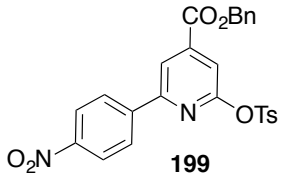
Methyl 2-{[(4-methylbenzene)sulfonyl]oxy}-6-[4-(trifluoromethyl)phenyl] pyridine-4-carboxylate



198

Following general procedure E, (phenylthio)acetic acid (168 mg, 1.0 mmol) and *i*-Pr_2NEt (260 μL, 1.50 mmol) in THF (15 mL) were added pivaloyl chloride (180 μL, 1.50 mmol) DHPB **86** (38 mg, 0.2 mmol), crude ketimine **182** (411 mg, 1.0 mmol) and *i*-Pr_2NEt (170 μL, 1.0 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 15:85), the title compound as a white solid (288 mg, 64%); mp 108-110 ^oC; ν_{max} (ATR)/cm^{-1} 1377 (SO_2), 1732 (C=O), 3094 (C-H); ^1H NMR (500 MHz, $CDCl_3$) 2.48 (3H, s, SO_2ArCH_3), 4.00 (3H, s, OCH_3), 7.37 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.63 (1H, s, py(3)*H*), 7.67 (2H, d, *J* 8.2, Ar(2,6)*H*), 7.89 (2H, d, *J* 8.2, Ar(3,5)*H*), 7.93 (2H, d, *J* 8.3, SO_2Ar (2,6)*H*), 8.24 (1H, s, py(5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 53.2 (CH_3), 114.5 (py$C(3)$H), 118.5 (py$C(5)$H), 123.8 (q, *J* 272, CF_3), 125.7 ($ArC(3,5)$H), 127.7 ($ArC(2,6)$H), 128.7 ($SO_2ArC(2,6)$H), 129.7 ($SO_2ArC(3,5)$H), 131.8 ($ArC(4)$), 134.0 ($SO_2ArC(4)$), 139.9 ($SO_2ArC(1)$), 142.8 ($ArC(1)$), 145.5 (py$C(6)$), 155.5 (py$C(4)$), 157.7 (py$C(2)$), 164.2 ($C(1)$); ^{19}F NMR (470 MHz, $CDCl_3$); −62.8 (CF_3); HRMS (NSI^+) $C_{21}H_{17}F_3NO_5S$ $[M+H]^+$, requires 452.0774 found 452.0766 (−1.8 ppm).

Benzyl 2-{[(4-methylbenzene)sulfonyl]oxy}-6-(4-nitrophenyl)pyridine-4-carboxylate

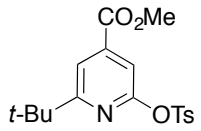


199

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (157 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol, 20 mol%), benzyl (2*E*)-4-(4-nitrophenyl)-4-(tosylimino)but-2-enoate (464 mg, 0.6 mmol) and *i*-Pr_2NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 15:85), the title compound as an orange solid (303 mg, 51 %), sample was recrystallised (Et_2O:Petrol) for analysis; mp 124-127 °C; ν_{max}

(ATR)/cm^{-1} 1165 (C-O), 1327 (SO_2), 1365, 1526 ($ArNO_2$), 1728 (C=O), 3062 (Ar-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.49 (3H, s, SO_2ArCH_3), 5.43 (2H, s, CO_2CH_2Ph), 7.36-7.47 (7H, m , Ar*H*), 7.67 (1H, s, py(5)*H*), 7.92-7.97 (4H, m, Ar*H*), 8.25-8.27 (3H, m, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 68.2 (CO_2CH_2Ph), 115.1 (py*C*(5)H), 118.9 (py*C*(3)H), 124.0 (Ar*C*H), 127.9 (Ar*C*H), 128.8-128.9 (Ar*C*H×4), 129.8 (Ar*C*H), 134.1 (SO_2ArC(1)), 134.7 (C(1)Ar*C*(1)), 142.4 (SO_2ArC(4)), 143.1 (py(6)Ar*C*(1)), 145.6 (py(6)Ar*C*(4)), 148.7 (py*C*(6)), 154.5 (py*C*(4)), 157.9 (py*C*(2)), 163.4 (C(1)); HRMS (NSI$^+$) $C_{26}H_{21}N_2O_7S^+$ ([M+H]$^+$) requires 505.1064 found 505.1056 (−1.6 ppm).

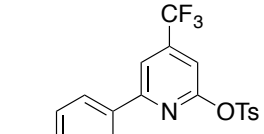
Methyl 2-tert-butyl-6-{[(4-methylbenzene)sulfonyl]oxy}pyridine-4-carboxylate



200

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (150 μL, 0.9 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22.8 mg, 0.12 mmol), ketimine **184** (194 mg, 0.6 mmol) and *i*-Pr_2NEt (100 μL, 0.6 mmol for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 15:85), the title compound as a brown solid (97 mg, 44%); mp 72-74 °C; ν_{max} (ATR)/cm^{-1} 1172, 1323 (S=O), 1371, 1730 (C=O), 2962 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 1.17 (9H, s, $(CH_3)_3$), 2.44 (3H, s, SO_2ArCH_3), 3.95 (3H, s, OCH_3), 7.33 (2H, d, *J* 7.5, SO_2Ar(3,5)*H*), 7.48 (1H, s, py(3)*H*), 7.75 (1H, s, py(5)*H*), 7.87 (2H, d, *J* 7.5, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (SO_2ArCH_3), 29.6 ($(CH_3)_3$), 37.7 ($C(CH_3)$), 52.9 (CH_3), 112.4 (py*C*(3)H), 117.4 (py*C*(5)H), 128.6 (SO_2ArC(2,6)H), 129.1 (SO_2ArC(3,5,)H), 134.1 (SO_2ArC(4)), 141.8 (SO_2ArC(1)), 145.1 (py*C*(6)), 156.7 (py*C*(4)), 164.8 (py*C*(2)), 170.2 (*C*(1)); HRMS (NSI$^+$) $C_{18}H_{22}NO_5S$ [M+H]$^+$ requires 364.1213 found 364.1214 (+0.2 ppm).

6-(4-Bromophenyl)-4-(trifluoromethyl)pyridin-2-yl 4-methylbenzene-1-sulfonate

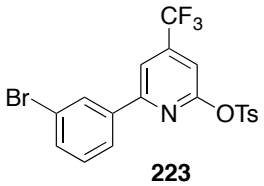


221

Following general procedure E, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), ketimine **217** (216 mg, 0.5 mmol), DHPB **86** (19.0 mg, 0.1 mmol) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol

10:90), the title compound as a white solid (146 mg, 62%); mp 134-136 °C; ν_{max} (ATR)/cm^{-1} 1146 (S=O), 1306 (S=O), 1564, 1591, 1614, 3110 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.51 (3H, s, C*H*$_3$), 7.26 (1H, s, C(3)*H*), 7.40 (2H, d, *J* 8.6, SO_2Ar(3,5)*H*), 7.56-7.60 (2H, m, C(6)Ar*H*), 7.65-7.68 (2H, m, C(6)Ar*H*), 7.81 (1H, s, *C*(5)*H*), 7.95-7.98 (2H, m, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (*C*H$_3$), 110.2 (q, *J* 3.5, (*C*(3)), 114.1 (q, *J* 3.2, *C*(5)), 122.0 (q, *J* 272, *C*F$_3$), 125.3 (C(6)Ar*C*(4)), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.8 (Ar*C*), 132.1 (Ar*C*), 134.0 (SO_2Ar*C*(1)), 135.1 (C(6)Ar*C*(1)), 143.3 (q, *J* 34.4, C(4)), 145.7 (SO_2Ar*C*(4)), 156.7 (*C*(6)), 157.5 (*C*(2)); ^{19}F NMR (470 MHz, $CDCl_3$); −64.5 (C*F*$_3$); HRMS (APCI$^+$) $C_{19}H_{14}{}^{79}BrF_3NO_3S$ [M+H]$^+$, requires 471.9824; found 471.9825 (+0.1 ppm).

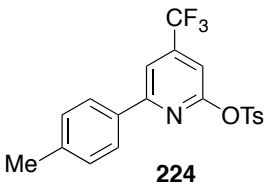
6-(3-Bromophenyl)-4-(trifluoromethyl)pyridine-2-yl-4-methylbenzne-1-sulfonate



223

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr$_2$NEt (210 μL, 1.2 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol), ketimine **216** (259 mg, 0.6 mmol) and *i*-Pr$_2$NEt (110 μL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et$_2$O:petrol 5:95), the title compound as a white solid (73 mg, 30%); mp 106-108 °C; ν_{max} (ATR)/cm^{-1} 1093 (Ar-Br), 1350 (SO_2), 3091 (Ar-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.50 (3H, s, SO_2ArC*H*$_3$), 7.28 (1H, s, pyC(3)*H*), 7.32 (1H, t, *J* 7.9, ArC(3)*H*), 7.43 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.58 (1H, d, *J* 8.0, ArC(2)*H*), 7.71 (1H, d, *J* 7.8, ArC(4)*H*), 7.77-7.83 (2H, m, Ar(5,6)*H*), 7.95 (2H, d, *J* 8.0, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$); 21.9 (SO_2Ar*C*H$_3$), 110.7 (py*C*(3)H), 114.4 (py*C*(5)H), 122.0 (q, *J* 275, *C*F$_3$), 123.3 (Ar*C*Br), 125.4 (Ar*C*(6)H), 128.8 (SO_2Ar*C*(2,6)H), 130.0 (SO_2Ar*C*(3,5)H), 130.2 (Ar*C*(4)H), 130.4 (Ar*C*(5)H), 133.4 (Ar*C*(2)H), 134.0 (SO_2Ar*C*(4)), 138.2 (Ar*C*(1)), 143.4 (py*C*(4)), 145.7 (SO_2Ar*C*(1)), 156.3 (py*C*(6)), 157.6 (py*C*(2)); ^{19}F NMR (470 MHz, $CDCl_3$); −64.6 (C*F*$_3$); HRMS (NSI$^+$) $C_{19}H_{14}{}^{79}BrF_3NO_3S$ [M+H]$^+$, requires 471.9824 found 471.9819 (−1.1 ppm).

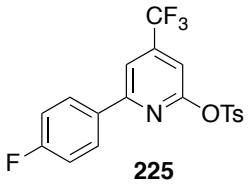
6-(4-Methylphenyl)-4-(trifluoromethyl)pyridine-2-yl-4-methylbenzne-1-sulfonate



224

Following general procedure E, (phenylthio)acetic acid (67 mg, 0.4 mmol) and *i*-Pr_2NEt (100 μL, 0.6 mmol) in THF (6 mL) were added pivaloyl chloride (74 μL, 0.9 mmol) DHPB **86** (15.2 mg, 0.08 mmol), ketimine **218** (147 mg, 0.4 mmol) and *i*-Pr_2NEt (79 μL, 0.4 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 5:95), the title compound as a white solid (97 mg, 60%); mp 124-126 °C; ν_{max} (ATR)/cm^{-1} 1346, 1368 (S=O), 3086 (Ar-H); ^1H NMR (500 MHz, $CDCl_3$) 2.44 (3H, s, ArC*H*$_3$) 2.51 (3H, s, SO_2ArCH_3), 7.22 (1H, s, pyC(3)*H*), 7.25 (2H, d, *J* 8.0, ArC(3)*H*), 7.40 (2H, d, *J* 8.6, SO_2ArC(3)*H*), 7.68 (2H, d, *J* 8.3, SO_2Ar(2)*H*), 7.81 (1H, s, py(5)*H*), 7.98 (2H, d, *J* 8.3, ArC(2)*H*); ^{13}C NMR (125 MHz, $CDCl_3$); 21.4 (Ar*C*H_3), 21.8 (SO_2ArCH_3), 109.3 (py*C*(3)H), 113.9 (py*C*(5)H), 122.0 (q, *J* 274, 633, *C*F_3), 127.0 (SO_2Ar*C*(2,6)H) 128.8 (Ar*C*(2,6)H), 129.6 (Ar*C*(3,5)H), 129.7 (SO_2Ar*C*(3,5)H), 133.5 (Ar*C*(4)), 134.1 (SO_2Ar*C*(4)), 140.9(Ar*C*(1)), 143.0 (SO_2Ar*C*(1)), 145.5 (py*C*(6)), 157.4 (py*C*(4)), 158.0 (py*C*(2)); ^{19}F NMR (470 MHz, $CDCl_3$); −64.6 (C*F*$_3$); HRMS (NSI^+) $C_{20}H_{17}F_3NO_3S$ $[M+H]^+$, requires 408.0876 found 408.0874 (−0.4 ppm).

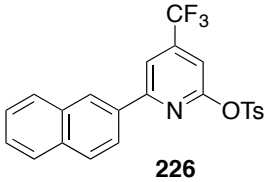
6-(4-Fluorophenyl)-4-(trifluoromethyl)pyridine-2-yl-4-methylbenzene-1-sulfonate



225

Following general procedure E, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (210 μL, 1.2 mmol) in THF (9 mL) were added pivaloyl chloride (110 μL, 0.9 mmol) DHPB **86** (22 mg, 0.12 mmol), ketimine **219** (223 mg, 0.6 mmol) and *i*-Pr_2NEt (110 mL, 0.6 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 5:95), the title compound as a yellow solid (114 mg, 45%); mp 99-102 °C; ν_{max} (ATR)/cm^{-1} 1170 (Ar-F), 1350 (S=O), 3094 (Ar-H); ^1H NMR (400 MHz, $CDCl_3$) 2.48 (3H, s, SO_2ArCH_3), 7.11 (2H, t, *J* 8.6, ArC(3,5)*H*), 7.21 (1H, s, pyC(3)*H*), 7.38 (2H, d, *J* 7.2, SO_2Ar(3,5)*H*), 7.74-7.79 (3H, m, py(5)*H* and Ar(2,6)*H*), 7.95 (2H, d, J 7.2, SO_2ArC(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 109.7 (py*C*(3)H), 113.9 (py*C*(5)H), 115.9 (d, *J* 21.9, Ar*C*(3,5)H), 122.0 (q, *J* 271, *C*F_3), 128.8 (SO_2Ar*C*(2,6)H), 129.1 (d, *J* 8.7, Ar*C*(2,6)H), 129.8 (SO_2Ar*C*(3,5)H), 132.4 (SO_2Ar*C*(4)), 134.0 (Ar*C*(1)), 143.2 (q, *J* 34.9, py*C*(4)), 145.6 (SO_2Ar*C*(1)), 156.8 (py*C*(6)), 157.4 (py*C*(4)), 164.3 (d, *J* 252, Ar*C*(4)); ^{19}F NMR (376 MHz, $CDCl_3$); −65.2 (C*F*$_3$), −110.5 (Ar*F*); HRMS (NSI^+) $C_{19}H_{14}F_4NO_3S$ $[M+H]^+$, requires 412.0625 found 412.0623 (−0.5 ppm).

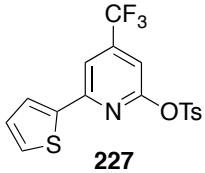
6-(Naphthalene-2-yl)-4-(trifluoromethyl)pyridine-2-yl 4-methylbenzene-1-sulfonate



226

Following general procedure E, (phenylthio)acetic acid (67 mg, 0.4 mmol) and *i*-Pr_2NEt (100 μL, 0.6 mmol) in THF (6 mL) were added pivaloyl chloride (74 μL, 0.6 mmol) DHPB **86** (15.2 mg, 0.08 mmol), ketimine **220** (161 mg, 0.4 mmol) and *i*-Pr_2NEt (79 μL, 0.4 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 10:90), the title compound as a yellow solid (82 mg, 46%); mp 112-114 °C; ν_{max} (ATR)/cm^{-1} 1344, 1371 (S=O), 3090 (Ar-H); ^1H NMR (500 MHz, $CDCl_3$) 2.49 (3H, s, SO_2ArCH_3), 7.26 (1H, s, py(3)*H*), 7.40 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.54-7.58 (2H, m, Np*H*), 7.83-7.90 (4H, m, Np*H*), 7.96 (1H, s, py(5)*H*), 7.99 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$), 8.24 (1H, s, Np(1)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 109.9 (py*C*(3)H), 114.5 (py*C*(5)H), 122.1 (*C*F_3), 123.9 (Np*C*H), 126.8 (Np*C*H), 127.3(Np*C*H), 127.5 (Np*C*H), 127.8 (Np*C*H), 128.7 (Np*C*H), 128.8 (Np*C*H), 128.9 ($SO_2ArC(2,5)H$), 129.8 ($SO_2ArC(3,5)H$), 133.2 ($SO_2ArC(4)$), 133.5 ($SO_2ArC(1)$), 134.1 (Np*C*), 134.2 (Np*C*), 143.2 (q, *J* 34.1, py*C*(4)), 145.5 (Np*C*(2)), 157.5 (py*C*(6)), 157.9 (py*C*(2)); ^{19}F NMR (470 MHz, $CDCl_3$) −64.6 (C*F*$_3$); HRMS (NSI^+) $C_{23}H_{17}F_3NO_3S$ $[M+H]^+$, requires 444.0876 found 444.0872 (−0.8 ppm).

6-(Thiophen-2-yl)-4-(trifluoromethyl)pyridine-2-yl-4-methylbenzne-1-sulfonate



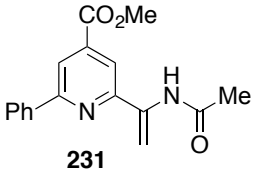
227

Following general procedure E, (phenylthio)acetic acid (67 mg, 0.4 mmol) and *i*-Pr_2NEt (100 μL, 0.4 mmol) in THF (6 mL) were added pivaloyl chloride (74 μL, 0.6 mmol) DHPB **86** (15.2 mg, 0.08 mmol), ketimine **221** (143 mg, 0.4 mmol) and *i*-Pr_2NEt (79 μL, 0.4 mmol) for 4 h at rt followed by heating at 80 °C for 16 h gave, after chromatographic purification (Et_2O:petrol 5:95), the title compound as a white solid (72 mg, 45%); mp 124-125 °C; ν_{max} (ATR)/cm^{-1} 1369 (S=O), 3098 (Ar-H); ^1H NMR (500 MHz, $CDCl_3$) 2.47 (3H, s, SO_2ArCH_3), 7.08-7.15 (2H, m, py(3)*H* and C(1)Ar(4)*H*), 7.39 (2H, d, *J* 8.0, $SO_2Ar(3,5)H$), 7.46 (1H, d, *J* 5.1, C(1)Ar(3)*H*), 7.57 (1H, d, *J* 3.8, C(1)Ar(5)*H*), 7.67 (1H, s, pyC(5)*H*), 8.00 (2H, d, *J* 8.2, $SO_2Ar(2,6)H$). ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 109.2 (py*C*(3)H), 112.8 (py*C*(5)H), 127.0 (C(1)Ar*C*(5)H) 127.9 (q, *J* 1345, 593, *C*F_3), 128.4 (C(1)Ar*C*(4)H) 128.9 ($SO_2ArC(2,6)H$), 129.7 (C(1)Ar*C*(3)H), 129.8 ($SO_2ArC(3,5)H$), 134.2 ($SO_2ArC(4)$), 141.7 (C(1)Ar*C*(1)), 143.1 (py*C*(4)), 145.6 ($SO_2ArC(1)$), 150.5 (py*C*(6)), 153.1 (py*C*(4)), 157.3 (py*C*(2)); ^{19}F NMR (470

MHz, $CDCl_3$) −64.8 (C*F*$_3$); HRMS (NSI^+) $C_{17}H_{13}F_3NO_3S_2$ $[M+H]^+$, requires 400.0283 found 400.0283 (−0.1 ppm).

9.2.7 Derivatisations

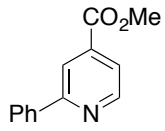
Methyl 2-(1-acetamidoethenyl)-6-phenylpyridine-4-carboxylate



231

Following the procedure of Gøgsig and co-workers.[170] A solution of **190** (115 mg, 0.3 mmol), *N*-vinylacetamide (102 mg, 1.2 mmol), *N*-methyldicyclohexylamine (193 μL, 0.9 mmol), DPPF (8.3 mg, 0.015 mmol) and [Pd(dba)$_2$] (8.6 mg, 0.015 mmol) were stirred in 1,4-dioxane (3 mL) in a screw top vial at 100 °C for 16 h. Once cooled, the reaction mixture was filtered through celite (eluent CH_2Cl_2) and concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 10:90) gave the title compound as a yellow solid (70 mg, 79%); mp 100-102 °C; ν_{max} (ATR)/cm^{-1} 1230, 1504, 1678 (C=O), 2949 (C-H), 3342 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.26 (3H, s, C*H*$_3$), 4.02 (3H, s, OC*H*$_3$), 5.72 (1H, s, =CH*H*), 6.62 (1H, s, =C*H*H), 7.48-7.57 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 8.03 (2H, dd, *J* 8.1, 1.4, Ar(2,6)*H*), 8.25 (2H, m, py(3)*H* and py(5)*H*), 9.35 (1H, s, N*H*) ^{13}C NMR (100 MHz, $CDCl_3$) 25.1 (*C*H$_3$), 53.0 (O*C*H$_3$), 100 (=*C*HH), 117.0 (py*C*(3)H), 119 (py*C*(5)H), 126.9 (py(6)Ar*C*(2,6)H), 129.0 (py(6)Ar*C*(4)H), 129.8 (py(6)Ar*C*(3,5)H), 136.7 (py(2)*C*=CH$_2$), 136.9 (py(6)Ar*C*(1)), 137.9 (py*C*(4)), 139.5 (py*C*(2)), 152.8 (py*C*(6)), 156.6 (*C*=O), 165.3 (NH*C*=O). HRMS (NSI^+) $C_{17}H_{16}N_2O_3$ $[M+H]^+$ requires 296.1161 found 296.1158 (+0.2 ppm).

Methyl 2-phenylpyridine-4-carboxylate



234

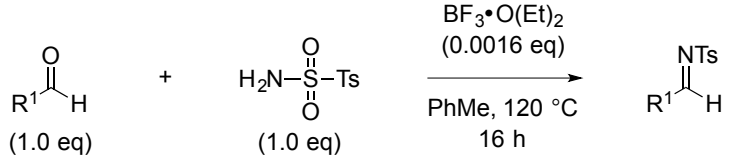
Following the procedure of Yoshida and co-workers.[80] To a solution of **190** (115 mg, 0.3 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5 mol%), DPPP (6.2 mg, 0.015 mmol, 5 mol%) and Et_3N (0.206 mL, 1.5 mmol) in DMF (2 mL) was added formic acid (34 μL, 0.9 mmol). The reaction was heated in a screw top vial for 1 h at 60 °C. Once cooled, the reaction mixture was quenched with brine and extracted with EtOAc (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 5:95) gave the title compound as a light pink oil (54 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) 3.98 (3 H, s, O*C*H$_3$), 7.26-7.51 (3 H, m, Ar(3,5)*H* and Ar(4)*H*), 7.76 (1 H, dd, *J*

5.0, 1.5, py(3)*H*), 8.03-8.06 (2 H, m, Ar(2,6)*H*), 8.29 (1 H, s, py(5)*H*), 8.83 (1 H, dd, *J* 5.0, 0.8, py(2)*H*). All data in accordance with literature.[171]

9.3 Experimental for Chapter 3

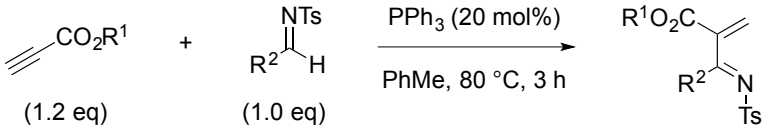
9.3.1 General Experimental Procedures

General Procedure F: *Preparation of aldimines*



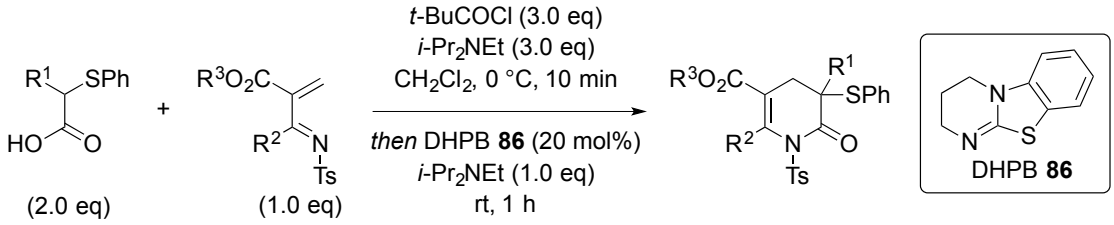
To a solution of requisite aldehyde (1.0 eq) and sulfonamide (1.0 eq) in toluene [0.33 M] at 120 °C using a Dean-Stark apparatus was added $BF_3.OEt_2$ (0.016 eq). The reaction was stirred at 120 °C until the theoretical amount of water was collected. The reaction mixture was quenched with aq. NaOH (2 M) extracted with EtOAc (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude reaction mixture. Products were purified by recrystallisation.

General Procedure G: *Preparation of 2-aryl-N-tosyliminoacrylates*



To a solution of requisite aldimine (1.0 eq) and triphenylphosphine (0.2 eq) in toluene [0.07 M in aldimine] at 80 °C was added a solution of requisite propiolate (1.2 eq) in toluene [0.24 M in propiolate] over 3 h. The reaction was concentrated under reduced pressure to give crude reaction mixture. Products were purified by column chromatography in the solvent system stated.

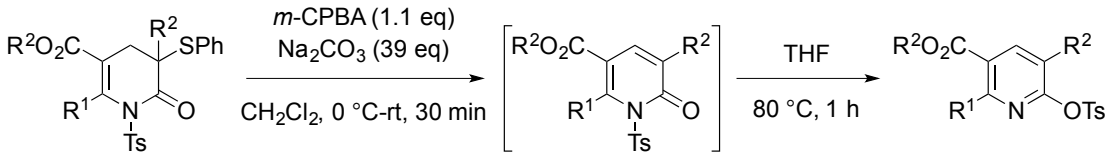
General Procedure H: *Isothiourea-catalyzed Michael addition/lactamisation*



To a solution of requisite acid (2.0 eq) in CH_2Cl_2 [0.06 M in imine] were added *i*-Pr_2NEt (3.0 eq) and pivaloyl chloride (3.0 eq) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 5 min. The requisite ketimine (1.0 eq), DHPB **86** (0.2 eq) and *i*-Pr_2NEt (1.0 eq) were added. The reaction mixture was stirred at rt until total consumption of ketimine as judged by TLC analysis.

The reaction mixture was quenched with aq. HCl (1 M), extracted with EtOAc (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude reaction mixture. Products were purified by column chromatography in the solvent system stated.

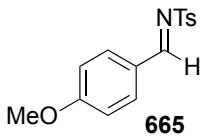
General Procedure I: *Oxidation-sulfoxide elimination/N- to O-sulfonyl transfer*



To a solution of dihydropyridinone in CH_2Cl_2 [0.04 M in dihydropyridinone] and Na_2CO_3 (39 eq) at 0 °C was added a solution of *m*-CPBA (1.1 eq) in CH_2Cl_2 [0.3 M in *m*-CPBA]. The reaction was warmed to rt and stirred for 30 min until total consumption of dihydropyridinone as judged by LC/MS or TLC analysis. The reaction mixture was quenched with sat. aq. $NaHCO_3$, extracted with EtOAc (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude intermediate pyridone. The residue was dissolved in THF and heated to 80 °C until total consumption of intermediate pyridone as judged by LC/MS or TLC analysis.

9.3.2 Preparation of Aldimines

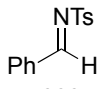
***N*-(4-Methoxybenzylidene)-4-methylbenzenesulfonamide**



665

Following general procedure F, benzaldehyde (2.54 mL, 25 mmol), *p*-toluenesulfonamide (4.28 g, 25.0 mmol) and $BF_3.OEt_2$ (37 μL, 0.4 mmol) in toluene (76 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.0 g, 77%): mp 128-130 °C {lit. 128-129 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.91 (3H, s, $ArOCH_3$), 6.99 (2H, d, *J* 8.7, Ar(3,5)*H*), 7.35 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.88-7.91 (4H, m, Ar(2,6)*H* and $SO_2Ar(2,6)H$), 8.97 (1H, s, C(1)*H*). All data in accordance with literature.[74]

***N*-Benzylidene-4-methylbenzenesulfonamide**

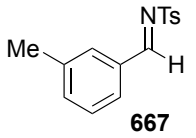


666

Following general procedure F, benzaldehyde (2.54 mL, 25 mmol), *p*-toluenesulfonamide (4.28 g, 25.0 mmol) and $BF_3.OEt_2$ (37 μL, 0.4 mmol) in toluene (76 mL) for 2 h at 120 °C gave, after recrystallization (EtOAc:isohexane), the title compound as a white solid (5.00 g, 77%): mp 110-

112 °C {lit. 111-112 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 7.35 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.49 (2H, t, *J* 7.7, Ar(3,5)*H*), 7.62 (1H, t, *J* 7.5, Ar(4)*H*), 7.91 (4H, m, Ar(2,6)*H* and $SO_2Ar(2,6)H$), 9.03 (1H, s, C(1)*H*). All data in accordance with literature.[74]

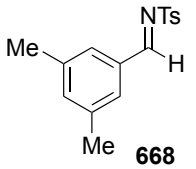
4-Methyl-*N*-(3-methylbenzylidene)benzenesulfonamide



667

Following general procedure F, 3-tolualdehyde (2.94 mL, 25.0 mmol), *p*-toluenesulfonamide (4.28 g, 25.0 mmol) and $BF_3.OEt_2$ (37 μL) in toluene (76 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.15 g, 80%); mp 89-90 °C {lit. 88-89 °C} ^{1}H NMR (400 MHz, $CDCl_3$) 2.40 (3H, s, SO_2ArCH_3), 2.45 (3H, s, $ArCH_3$), 7.31-7.44 (4H, m, $SO_2Ar(3,5)H$) and Ar(5)*H* and Ar(4)*H*), 7.71 (1H, d, *J* 7.3, Ar(6)*H*), 7.77 (1H, Ar(2)*H*), 7.90 (2H, d, *J* 7.9, $SO_2Ar(2,6)H$), 9.01 (1H, s, C(1)*H*). All data in accordance with literature.[172]

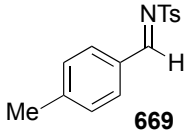
***N*-(3,5-Dimethylbenzylidene)-4-methylbenzenesulfonamide**



668

Following general procedure F, 3,5-dimethylbenzaldehyde (3.0 mL, 22.4 mmol), *p*-toluenesulfonamide (3.84 g, 22.4 mmol) and $BF_3.OEt_2$ (33 μL) in toluene (68 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.15 g, 80%): mp 101-103 °C ^{1}H NMR (400 MHz, $CDCl_3$) 2.35 (6H, s, Ar(3)CH_3 and Ar(5)CH_3), 2.43 (3H, s, SO_2ArCH_3), 7.24 (1H, s, Ar(4)*H*), 7.34 (2H, d, *J* 7.8, $SO_2Ar(3,5)H$), 7.54 (2H, s, Ar(2,6)*H*), 7.88 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$), 8.96 (1H, s, C(1)*H*). All data in accordance with literature.[173]

4-Methyl-*N*-(4-methylbenzylidene)benzenesulfonamide

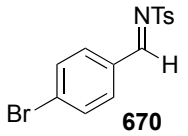


669

Following general procedure F, *p*-tolualdehyde (2.94 mL, 25 mmol), *p*-toluenesulfonamide (4.28 g, 25 mmol) and $BF_3.OEt_2$ (37 μL, 0.4 mmol) in toluene (76 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.80 g, 85%): mp 112-114 °C {lit. 114-116 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.43-2.44 (6H, m, SO_2ArCH_3 and

ArC*H*$_3$), 7.29 (2H, d, *J* 8.0, Ar(3,5)*H*), 7.34 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.82 (2H, d, *J* 8.2, Ar(2,6)*H*), 7.88 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.99 (1H, s, C(1)*H*). All data in accordance with literature.[174]

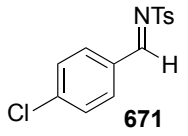
_N_-(4-Bromobenzylidene)-4-methylbenzenesulfonamide



670

Following general procedure F, 4-bromobenzaldehyde (3.00 g, 16.2 mmol), *p*-toluenesulfonamide (2.77 g, 16.2 mmol) and $BF_3.OEt_2$ (24 μL) in toluene (50 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (4.90 g, 90%); mp 188-189 °C {lit. 190 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArC*H*$_3$), 7.35 (2H, d, *J* 8.5, SO_2Ar(3,5)*H*), 7.63 (2H, d, *J* 8.5, Ar(3,5)*H*), 7.78 (2H, d, *J* 8.5, SO_2Ar(2,6)*H*), 7.88 (2H, d, *J* 8.3, Ar(2,6)*H*), 8.98 (1H, s, C(1)*H*). All data in accordance with literature.[175]

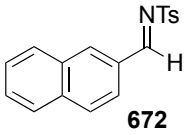
_N_-(4-Chlorobenzylidene)-4-methylbenzenesulfonamide



671

Following general procedure F, 4-chlorobenzaldehyde (3.00 g, 21.3 mmol), *p*-toluenesulfonamide (3.65 g, 21.3 mmol) and $BF_3.OEt_2$ (31 μL) in toluene (65 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.26 g, 84%); mp 175-177 °C {lit. 175-176 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArC*H*$_3$), 7.36 (2H, d, *J* 7.8, SO_2Ar(3,5)*H*), 7.47 (2H, d, *J* 8.3, Ar(3,5)*H*), 7.86-7.90 (4H, m, SO_2Ar(2,6)*H* and Ar(2,6)*H*), 9.00 (1H, s, C(1)*H*). All data in accordance with literature.[74]

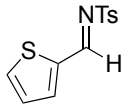
4-Methyl-_N_-(naphthalen-2-ylmethylene)benzenesulfonamide



672

Following general procedure F, 2-naphthaldehyde (3.00 g, 19.2 mmol), *p*-toluenesulfonamide (3.29 g, 19.2 mmol) and $BF_3.OEt_2$ (28 μL, 0.31 mmol) in toluene (58 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (5.23 g, 88%); mp 116-117 °C {lit. 114-116 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArC*H*$_3$), 7.37 (2H, *J* 8.4, Ar*H*), 7.57 (1H, t, *J* 7.1, Ar*H*), 7.62 (1H, t, *J* 7.1), 7.87 (2H, d, *J* 8.8, Ar*H*), 7.91-7.99 (3H, m, Ar*H*), 8.01 (1H, dd, *J* 8.4, 1.3, Ar*H*), 8.32 (1H, s, Ar*H*), 9.17 (1H, s, C(1)*H*). A|ll data in accordance with literature.[176]

4-Methyl-*N*-(thiophen-2-ylmethylene)benzenesulfonamide

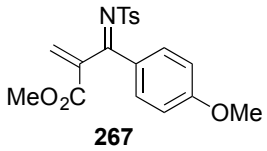


673

Following general procedure F, 2-thiophene carboxaldehyde (2.50 mL, 26.7 mmol), *p*-toluenesulfonamide (4.57 g, 26.7 mmol) and $BF_3.OEt_2$ (39 µL, 0.43 mmol) in toluene (81 mL) for 2 h at 120 °C gave, after recrystallisation (EtOAc:isohexane), the title compound as a white solid (4.46 g, 63%); mp 99-100 °C {lit.[175] 98 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 7.21 (1H, t, *J* 4.4, Ar(4)*H*), 7.34 (2H, d, *J* 7.9, $SO_2Ar(3,5)H$), 7.78 (2H, m, Ar(2)*H* and Ar(5)*H*), 7.87 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$), 9.11 (1H, s, C(1)*H*). All data in accordance with literature.[175]

9.3.3 Preparation of 2-Aryl(tosylimino) acrylates

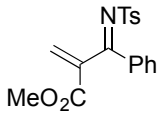
Methyl 2-((4-methoxyphenyl)(tosylimino)methyl)acrylate



267

Following general procedure G, aldimine **665** (1.00 g, 3.48 mmol), triphenylphosphine (184 mg, 0.70 mmol) in toluene (50 mL) and methyl propiolate (0.37 mL, 4.18 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95) the title compound as yellow oil (910 mg, 70%); ^{1}H NMR (400 MHz, CDCl3) 2.43 (3H, s, SO_2ArCH_3), 3.78 (3H, s, $ArOCH_3$), 3.85 (3H, s, CO_2CH_3), 5.87 (1H, s, =C*H*H), 6.80 (1H, s, =CH*H*), 6.88 (2H, d, *J* 9.0, Ar(3,5)*H*), 7.32 (2H, d, *J* 8.0, $SO_2Ar(3,5)H$), 7.82-7.88 (4H, m, $SO_2Ar(2,6)H$ and Ar(2,6)*H*). All data in accordance with literature.[86]

Methyl 2-(phenyl(tosylimino)methyl)acrylate

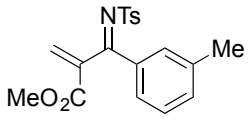


263

Following general procedure G, aldimine **666** (1.0 g, 3.89 mmol), triphenylphosphine (204 mg, 0.78 mmol) in toluene (58 mL) and methyl propiolate (0.42 mL, 4.7 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95), the title compound as a colourless oil (534 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) 2.47 (3H, s, SO_2ArCH3), 3.81 (3H, s, CO_2CH_3), 5.96 (1H, s, =C*H*H), 6.86 (1H, s, =CH*H*), 7.37 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.44 (2H, t, *J* 7.9, Ar(3,5)*H*), 7.59 (1H, t, *J* 7.4, Ar(4)*H*), 7.88-7.93 (4H, m,

Ar(2,6)*H* and SO_2Ar(2,6)*H*). All data in accordance with literature.[86]

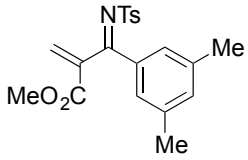
Methyl 2-(*m*-tolyl(tosylimino)methyl)acrylate



284

Following general procedure G, aldimine **667** (1.50 g, 5.53 mmol), triphenylphosphine (290 mg, 1.11 mmol) in toluene (91 mL) and methyl propiolate (0.59 mL, 6.64 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 25:75) the title compound as white solid (1.03 mg, 52%); mp 90-91 °C; ν_{max} (ATR)/cm^{-1} 1147 (S=O), 1433 (C-O), 1566 (C=N), 1732 (C=O), 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.36 (3H, s, ArC*H*$_3$), 2.44 (3H, s, SO_2ArC*H*$_3$), 3.78 (3H, s, CO_2C*H*$_3$), 5.90 (1H, s, =C*H*H), 6.82 (1H, s, =CH*H*), 7.27-7.37 (4H, m, Ar(4)*H* and Ar(5)*H*) and SO_2Ar(3,5)*H*), 7.64 (1H, br. d, *J* 7.8, Ar(6)*H*), 7.68 (1H, br. s, Ar(2)*H*), 7.89 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (Ar*C*H$_3$), 21.8 (SO_2Ar*C*H$_3$), 52.7 (CO_2*C*H$_3$), 127.4 (Ar*C*(6)), 127.8 (SO_2Ar*C*(2,6)H), 128.7 (Ar*C*(5)H), 129.6 (SO_2Ar*C*(3,5)H), 130.2 (Ar*C*(2)H), 130.6 (=*C*HH), 135.0 (Ar*C*(4)H), 135.7 (SO_2Ar*C*(4)), 137.3 (*C*(2)), 137.7 (Ar*C*(1)), 138.7 (Ar*C*(3)), 144.0 (SO_2Ar*C*(1), 163.7 (*C*(1)), 174.0 (*C*O_2Me); HRMS (NSI$^+$) $C_{19}H_{19}NO_4S$ ([M+H]$^+$) requires 358.1113 found 358.1103 (−1.3 ppm).

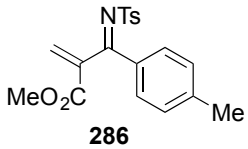
Methyl 2-((3,5-dimethylphenyl)(tosylimino)methyl)acrylate



285

Following general procedure G, aldimine **668** (1.00 g, 3.51 mmol), triphenylphosphine (184 mg, 0.70 mmol) in toluene (50 mL) and methyl propiolate (0.37 mL, 4.21 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95) the title compound as yellow oil (833 mg, 64%); ν_{max} (ATR)/cm^{-1} 1149 (S=O), 1312 (C-O), 1551 (C=N), 1728 (C=O), 2924, 3020 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.31 (6H, s, Ar(3)C*H*$_3$ and Ar(5)C*H*$_3$), 2.46 (3H, s, SO_2ArC*H*$_3$), 3.78 (3H, s, CO_2C*H*$_3$), 5.87 (1H, s, =C*H*H), 6.81 (1H, s, =CH*H*), 7.19 (1H, br. s, Ar(4)*H*), 7.34 (2H, d, *J* 7.8, SO_2Ar(3,5)*H*), 7.46 (2H, br. s, Ar(2,6)*H*), 7.88 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.3 (Ar(3)*C*H$_3$ and Ar(5)*C*H$_3$), 21.8 (SO_2Ar*C*H$_3$), 52.7 (CO_2*C*H$_3$), 127.7 (Ar*C*(2,6)H), 127.8 (SO_2Ar*C*(2,6)H), 129.6 (SO_2Ar*C*(3,5,)H), 130.4 (=*C*HH), 135.8 (*C*(2)), 136.0 (Ar*C*(4)H), 137.4 (Ar*C*(1)), 137.8 (SO_2Ar*C*(4)), 138.5 (Ar*C*(3) and Ar*C*(5)), 144.0 (SO_2Ar*C*(1)), 163.8 (C(1)), 174.3 (*C*O_2Me); HRMS (NSI$^+$) $C_{20}H_{22}NO_4S$ ([M+H]$^+$) requires 372.1264 found 372.1257 (−2.0 ppm).

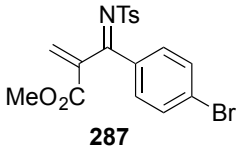
Methyl 2-(4-tolyl(tosylimino)methyl)acrylate



286

Following general procedure G, aldimine **669** (1.00 g, 3.69 mmol), triphenylphosphine (194 mg, 0.74 mmol) in toluene (54 mL) and methyl propiolate (0.39 mL, 4.43 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95) the title compound as yellow oil (791 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) 2.39, (3H, s, ArC*H*$_3$), 2.44 (3H, s, SO_2ArC*H*$_3$), 3.78 (3H, s, ArC*H*$_3$), 3.77 (3H, s, CO_2C*H*$_3$), 5.89 (1H, s, =C*H*H), 6.81 (1H, s, =CH*H*), 7.20 (2H, d, *J* 8.1, Ar(3,5)*H*), 7.33 (2H, d, *J* 7.9, SO_2Ar(3,5)*H*), 7.76 (2H, d, *J* 8.3, Ar(2,6)*H*), 7.88 (2H, d, *J* 8.30, SO_2Ar(2,6)*H*). All data in accordance with literature.[86]

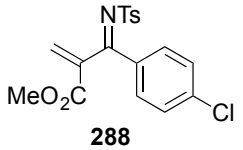
Methyl 2-((4-bromophenyl)(tosylimino)methyl)acrylate



287

Following general procedure G, aldimine **670** (1.50 g, 4.44 mmol), triphenylphosphine (233 mg, 0.89 mmol) in toluene (69 mL) and methyl propiolate (0.47 mL, 5.32 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95) the title compound as colourless oil (788 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$), 2.44 (3H, s, SO_2Ar(C*H*$_3$)), 3.78 (3H, s, CO_2C*H*$_3$), 5.93 (1H, s, =C*H*H), 6.82 (1H, s, =CH*H*), 7.32 (2H, d, *J* 8.0, Ar(3,5)*H*), 7.52 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.70 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*), 7.86 (2H, d, *J* 8.2 Ar(2,6)*H*). All data in accordance with literature.[86]

Methyl 2-((4-chlorophenyl)(tosylimino)methyl)acrylate

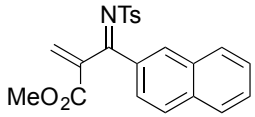


288

Following general procedure G, aldimine **671** (1.00 g, 3.42 mmol), triphenylphosphine (179 mg, 0.68 mmol) in toluene (48 mL) and methyl propiolate (0.37 mL, 4.11 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95, R_f = 0.20) the title compound as yellow oil (491 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$), 2.46 (3H, s, SO_2Ar(C*H*$_3$)), 3.79 (3H, s, CO_2C*H*$_3$), 5.93 (1H, s, =C*H*H), 6.78 (1H, s, =CH*H*), 7.34 (2H, d, *J*

7.9, Ar(3,5)*H*), 7.38 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.79 (2H, d, *J* 8.6, SO_2Ar(2,6)*H*), 7.88 (2H, d, *J* 8.3 Ar(2,6)*H*). All data in accordance with literature.[86]

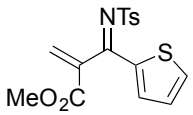
Methyl 2-(naphthalen-2-yl(tosylimino)methyl)acrylate



290

Following general procedure G, aldimine **672** (1.50 g, 4.85 mmol), triphenylphosphine (254 mg, 0.97 mmol) in toluene (79 mL) and methyl propiolate (0.52 mL, 5.82 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 5:95) the title compound as white solid (788 mg, 42%); mp 128-131 °C ν_{max} (ATR)/cm^{-1} 1149 (S=O), 1304 (C-O), 1551 (C=N), 1736 (C=O), 2947, 3055 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2Ar(C*H*$_3$)), 3.79 (3H, s, CO_2C*H*$_3$), 5.99 (1H, s, =C*H*H), 6.92 (1H, s, =CH*H*), 7.36 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.53 (1H, ddd, *J* 8.2, 6.9, 1.3, Ar*H*), 7.60 (1H, ddd, *J* 8.2, 6.8, 1.4, Ar*H*), 7.82-7.90 (3H, m, Ar*H* and Ar*H* and Ar*H*), 7.94 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.03 (1H, dd, *J* 8.8, 1.9, Ar*H*), 8.27 (1H, s, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.7 (SO_2Ar*C*H$_3$), 52.8 (CO_2*C*H$_3$), 124.4 (Ar*C*H), 127.1 (Ar*C*H), 127.7 (SO_2Ar*C*(2,6)H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 129.2 (Ar*C*H), 129.6 (SO_2Ar*C*(3,5)H), 129.8 (Ar*C*H), 130.9 (=*C*HH), 132.4 (Ar*C*), 133.1 (Ar*C*H), 136.0 (Ar*C*), 137.2 (Ar*C*), 137.8 (SO_2Ar*C*(4)), 144.1 (SO_2Ar*C*(1)), 163.7 (*C*(1)), 173.6 (*C*O_2Me); HRMS (NSI^+) $C_{22}H_{20}NO_4S$ ($[M+H]^+$) requires 394.1108 found 394.1105 (−0.6 ppm).

Methyl 2-(thiophen-2-yl(tosylimino)methyl)acrylate

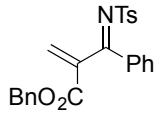


291

Following general procedure G, aldimine **673** (1.50 g, 5.65 mmol), triphenylphosphine (296 mg, 1.13 mmol) in toluene (93 mL) and methyl propiolate (0.60 mL, 6.78 mmol) in toluene (20 mL) for 3 h at 80 °C gave, after preparative HPLC (MeCN:H_2O with 10 mM ammonium acetate), the title compound as yellow oil (631 mg, 32%); ν_{max} (ATR)/cm^{-1} 1146 (S=O), 1323 (C-O), 1545 (C=N), 1743 (C=O), 2949, 3065 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.41 (3H, s, SO_2ArC*H*$_3$), 3.79 (3H, s, CO_2C*H*$_3$), 5.92 (1H, s, =C*H*H), 6.77 (1H, s, =CH*H*), 7.09 (1H, dd, *J* 5.0, 3.9, Ar(4)*H*), 7.30 (2H, d, *J* 8.3, SO_2Ar(3,5)*H*), 7.55 (1H, dd, *J* 3.9, 1.2, Ar(3)*H*), 7.69 (1H, dd, *J* 4.9, 1.2, Ar(5)*H*), 7.84 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.7 (SO_2Ar*C*H$_3$), 52.7 (CO_2*C*H$_3$), 127.6 (SO_2Ar*C*(2,6)H), 128.8 (Ar*C*(4)H), 129.6 (SO_2Ar*C*(3,5)H), 130.3 (=*C*HH), 136.6 (Ar*C*(5)H), 136.6 (Ar*C*(3)H), 137.1 (Ar*C*(2)), 137.6 (*C*(2)), 142.8

($SO_2ArC(4)$), 144.0 ($SO_2ArC(1)$), 163.4 ($C(1)$), 167.0 (CO_2Me); HRMS (NSI^+) $C_{16}H_{16}NO_4S_2$ ($[M+H]^+$) requires 350.0515 found 350.0518 (+0.8 ppm).

Benzyl 2-(phenyl(tosylimino)methyl)acrylate

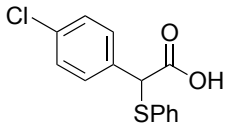


296

Following general procedure G, aldimine **666** (5.00 g, 19.3 mmol), triphenylphosphine (1.01 mg, 3.86 mmol) in toluene (603 mL) and benzyl propiolate (3.72 g, 23.2 mmol) in toluene (40 mL) for 3 h at 80 °C gave, after column chromatography (EtOAc:isohexane 15:85) the title compound as colourless oil (1.21 g, 15%); ^1H NMR (400 MHz, $CDCl_3$), 2.43 (3H, s, SO_2ArCH_3), 5.26 (2H, s, CO_2CH_2Ph), 5.99 (1H, s, =C*H*H), 6.88 (1H, s, =CH*H*), 7.23-7.30 (3H, m,), 7.38-7.42 (6H, m,), 7.44 (1H, t, *J* 7.6,), 7.86 (4H, d, *J* 6.8,) All data in accordance with literature.[86]

9.3.4 Preparation of α,α-Disubstituted Acetic Acids

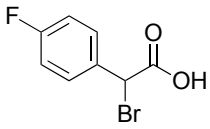
2-(4-Chlorophenyl)-2-(phenylthio)acetic acid



328

To a solution of 2-Bromo-2-(4-chlorophenyl)acetic acid (1.50 g, 6.01 mmol) and K_2CO_3 (4.99 g, 36.1 mmol) in 1,4-dioxane (20 mL) was added thiophenol (1.84 mL, 18.0 mmol) and reaction stirred at 80 °C for 16 h. Reaction diluted with H_2O (50 mL) and extracted with EtOAc (×3). The aqueous layers were combined and acidified with aq. HCl (6 M) and extracted with EtOAc (×3), combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. Crude product gave, following recrystallisation (Et_2O:hexane), the title compound as brown solid (709 mg, 42%): mp 91-93 °C {lit. 92.5-93.5 °C}; ^1H NMR (500 MHz, $CDCl_3$) 4.75 (1H, s, C(2)*H*), 7.17-7.20 (5H, m, Ar*H*), 7.26-7.28 (4H, m, Ar*H*), 11.0 (1H, br. s, CO_2H). All data in accordance with literature.[177]

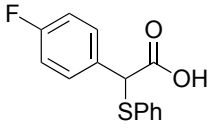
2-Bromo-2-(4-fluorophenyl)acetic acid



325

To a solution of 4-fluorophenylacetic acid (3.00 g, 19.5 mmol) in CCl_4 at 70 °C, was added NBS (6.94 g, 93.0 mmol) and benzoyl peroxide (25 mg, 0.08 mmol) and reaction stirred for 16 h under UV irradiation. Reaction mixture concentrated under reduced pressure and carried forward without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) 5.35 (1H, s, C(2)*H*), 7.04-7.08 (2H, m, Ar(3,6)*H*), 7.54-7.57 (2H, m, Ar(2,6)*H*), 11.5 (1H, s, CO_2H).

2-(4-Fluorophenyl)-2-(phenylthio)acetic acid

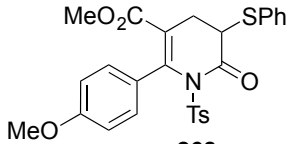


326

To a solution of 2-bromo-2-(4-fluorophenyl)acetic acid **325** (1.55 g, 6.64 mmol) and K_2CO_3 (1.84 g, 13.3 mmol) in 1,4-dioxane (22 mL) was added thiophenol (0.745 mL, 7.30 mmol) and reaction stirred at 80 °C for 16 h. Reaction diluted with H_2O (50 mL) and extracted with EtOAc (×3). The aqueous layers were combined and acidified with aq. HCl (6 M) and extracted with EtOAc (×3), combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to give residue of 80-90% purity which was carried forward without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) 4.90 (1H, s, C(2)*H*), 7.03-7.07 (2H, m, C(2)Ar(3,5)*H*), 7.31-7.36 (3H, m, SAr(3,5)*H* and SAr(4)*H*), 7.51-7.54 (4H, m, C(2)Ar(2,6)*H* and SAr(2,6)*H*), 10.7 (1H, br. s, CO_2H).

9.3.5 Isothiourea-Catalysed Michael Addition/Lactamisation

Methyl 2-(4-methoxyphenyl)-6-oxo-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

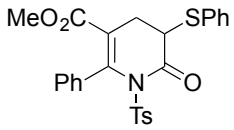


268

Following general procedure H, (phenylthio)acetic acid (252 mg, 1.5 mmol) and *i*-Pr_2NEt (0.39 mL, 2.25 mmol) were added pivaloyl chloride (0.28 mL, 2.25 mmol), DHPB **86** (29 mg, 0.15 mmol), ketimine **267** (280 mg, 0.75 mmol) and *i*-Pr_2NEt (0.13 mL, 0.75 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 10:90) the title compound as colourless oil (267 mg, 68%); ν_{max} (ATR)/cm^{-1} 1147 (S=O), 1340 (C-O), 1718 (C=O), 3004 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.41 (3H, s, SO_2ArCH_3), 2.94 (1H, dd, *J* 15.8, 5.8, C(4)*H*H), 3.08 (1H, dd, *J* 15.8, 4.2, C(4)H*H*), 3.56 (3H, s, CO_2CH_3), 3.84 (3H, s, $ArOCH_3$), 3.93 (1H, dd, *J* 5.7, 4.1, C(5)*H*), 6.80 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.14-7.18 (4H, m, SAr(3,5)*H* and SO_2Ar(3,5)*H*), 7.29-7.32 (3H, m, SAr(4)*H* and SAr(2,6)*H*), 7.46-7.52 (4H, m, SO_2Ar(2,6)*H* and

C(2)Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 29.1 (*C*(4)HH), 51.2 (*C*(5)H), 52.1 (CO_2CH_3), 55.4 ($ArOCH_3$), 113.0 (C(2)Ar*C*(3,5)H), 118.6 (*C*(3)), 126.3 (C(2)Ar*C*(1)), 128.6 (SAr*C*(4)H), 128.9 (SO_2ArC(2,6)H), 129.2 (SAr*C*(2,6)H), 129.4 (SO_2ArC(3,5)H), 130.9 (SAr*C*(3,5)H), 132.4 (SAr*C*(1)), 133.2 (C(2)Ar*C*(2,6)H), 136.3 (SO_2ArC(4)), 145.2 (SO_2Ar(1)), 145.5 (*C*(2)), 160.3 (C(2)Ar*C*(4)), 166.6 (CO_2Me), 169.8 (*C*(6)); HRMS (NSI$^+$) $C_{27}H_{26}NO_6S_2$ ([M+H]$^+$) requires 524.1196 found 524.1191 (−1.0 ppm).

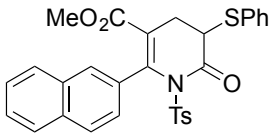
Methyl 6-oxo-2-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



264

Following general procedure H, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **263** (103 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.75 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (101 mg, 68%); mp 138-140 °C ν_{max} (ATR)/cm^{-1} 1141 (S=O), 1366 (C-O), 1713 (C=O), 3055 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.40 (3H, s, SO_2ArCH_3), 2.96 (1H, dd, *J* 15.9, 5.6 C(4)*H*H), 3.12 (1H, dd, *J* 15.9, 4.2 C(4)H*H*), 3.53 (3H, s, CO_2CH_3), 3.96 (1H, dd, *J* 5.6, 4.2, C(5)*H*), 7.15 (2H, d, *J* 8.3, SO_2Ar(3,5)H), 7.21-7.23 (2H, m, SAr(3,5)*H*), 7.28-7.32 (5H, m, SAr(4)*H* and SAr(2,6)*H* and Ar(3,5)*H*), 7.35-7.40 (1H, m, Ar(4)*H*), 7.43-7.51 (4H, m, SO_2Ar(2,6)*H* and Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 29.1 (*C*(4)HH), 51.0 (*C*(5)H), 52.1 (CO_2CH_3), 119.3 (*C*(3)), 127.5 (SAr*C*(4)H), 128.6 (SAr*C*(3,5)H), 128.9 (SO_2ArC(2,6)H), 129.1 (Ar*C*(4)H), 129.3 (SO_2ArC(3,5)H), 129.4 (Ar*C*(3,5)H), 129.5 (SAr*C*(2,6)H), 132.3 (SAr*C*(1)), 133.2 (Ar*C*(2,6)H), 133.9 (SO_2ArC(4)), 136.1 (Ar*C*(1)), 145.2 (SO_2ArC(1)), 145.3 (*C*(2)), 166.4 (CO_2Me), 169.7 (*C*(6)); HRMS (NSI$^+$) $C_{26}H_{24}NO_5S_2$ ([M+H]$^+$) requires 494.1090 found 494.1084 (−1.3 ppm).

Methyl 2-(naphthalen-2-yl)-6-oxo-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

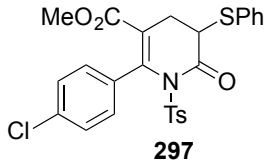


296

Following general procedure H, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **290** (118 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.75 mmol) for 4 h at rt gave,

after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (101 mg, 62%): 117-118 °C; ν_{max} (ATR)/cm^{-1} 1089 (S=O), 1368 (C-O), 1715 (C=O), 2949, 3048 (C-H); δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, SO_2ArCH_3), 3.03 (1H, dd, *J* 15.8, 5.7, C(4)*H*H), 3.19 (1|H, dd, *J* 15.8, 4.2, C(4)H*H*), 3.50 (3H, s, CO_2CH_3), 4.04 (1H, dd, *J* 5.6, 4.2, C(5)*H*), 6.90 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.29-7.34 (5H, m, Ar*H*), 7.38 (1H, br. s, Ar*H*), 7.42-7.47 (2H, m, Ar*H*), 7.52-7.55 (4H, m, Ar*H*), 7.79 (1H, d, *J* 8.6, SO_2Ar(2,6)*H*), 7.84-7.87 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.7 (SO_2ArCH_3), 29.2 (*C*(4)HH), 51.2 (*C*(5)H), 52.1 (CO_2CH_3), 119.2 (*C*(3)), 126.2 (Ar*C*H), 126.8 (SO_2Ar(2,6)H), 127.0 (Ar*C*H), 127.9 (Ar*C*H), 128.0 (Ar*C*H), 128.0 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*H), 129.4 (Ar*C*H), 131.3 (Ar*C*), 132.3 (Ar*C*), 132.4 (Ar*C*), 133.2 (Ar*C*H), 133.4 (Ar*C*), 136.1 (Ar*C*), 145.1 (SO_2ArC(1)), 145.7 (*C*(2)), 166.3 (CO_2Me), 169.8 (*C*(6)); HRMS (NSI^+) $C_{30}H_{26}NO_5S_2$ ($[M+H]^+$) requires 544.1247 found 544.1245 (−0.4 ppm).

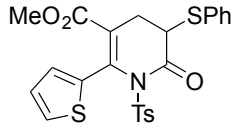
(Phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



297

Following general procedure H, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **288** (113 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.75 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) the title compound as 90% pure brown oil which was carried forward without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) 2.42 (3H, s, SO_2ArCH_3), 2.97 (1H, dd, *J* 15.9, 5.4 C(4)*H*H), 3.10 (1H, dd, *J* 15.9, 4.2 C(4)H*H*), 3.56 (3H, s, CO_2CH_3), 3.95 (1H, t, *J* 4.7, C(5)*H*), 7.15-7.20 (4H, m, SO_2(3,5)*H* and SAr(3,5)*H*), 7.24-7.31 (5H, m, Ar(2,6)*H* and SAr(2,6)*H* and SAr(4)*H*), 7.46-7.50 (4h, m, SO_2Ar(2,6)*H* and Ar(3,5)*H*).

Methyl 6-oxo-5-(phenylthio)-2-(thiophen-2-yl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

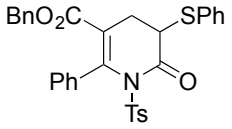


298

Following general procedure H, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06

mmol), ketimine **291** (105 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.75 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as yellow oil (99 mg, 66%); ν_{max} (ATR)/cm^{-1} 1149 (S=O), 1310 (C-O), 1712 (C=O), 2877, 2955 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.42 (3H, s, SO_2ArCH_3), 2.92 (1H, dd, *J* 15.9, 6.1, C(4)*H*H), 3.05 (1H, dd, *J* 15.9, 4.2, C(4)H*H*), 3.63 (3H, s, CO_2CH_3), 3.93 (1H, dd, *J* 6.0, 4.3, C(5)*H*), 6.98 (1H, dd, *J* 4.9, 3.7, C(2)Ar(4)*H*), 7.08-7.09 (1H, m, C(2)Ar(3)H), 7.20 (2H, d, *J* 8.2, $SO_2Ar(3,5)H$), 7.26-7.31 (3H, m, C(5)Ar(4)*H* and C(5)Ar(3,5)*H*), 7.40 (1H, d, *J* 5.0, C(2)Ar(5)*H*), 7.46-7.49 (2H, m, C(5)Ar(2,6)*H*), 7.61 (2H, *J* 8.3, $SO_2Ar(2,6)H$); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 29.4 (*C*(4)HH), 50.9 (*C*(5)H), 52.4 (CO_2CH_3), 121.4 (*C*(3)), 126.3 (C(5)Ar*C*(4)H), 128.0 (C(2)Ar*C*(3)H), 128.7 (C(2)Ar*C*(4)H), 128.9 (C(5)Ar*C*(3,5)H), 129.4 ($SO_2ArC(3,5)H$), 129.4 (C(5)Ar*C*(2,6)H), 130.6 (C(2)Ar*C*(5)H), 132.0 (C(5)Ar*C*(1)), 133.5 ($SO_2ArC(2,6)H$), 134.6 ($SO_2ArC(4)$), 136.2 (C(2)Ar*C*(2)), 138.3 ($SO_2ArC(1)$), 145.3 (*C*(2)), 166.2 (*C*O_2Me), 169.3 (*C*(6)); HRMS (NSI^+) $C_{24}H_{22}NO_5S_3$ ($[M+H]^+$) requires 500.0655 found 500.0648 (−1.3 ppm).

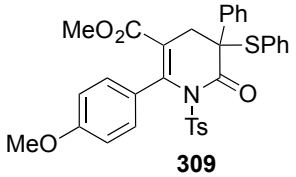
Benzyl 6-oxo-2-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



299

Following general procedure H, (phenylthio)acetic acid (101 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **263** (126 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.75 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:Petrol 15:85), the title compound as 90% pure brown oil which was carried forward without further purification: ^1H NMR (500 MHz, $CDCl_3$) 2.40 (3H, s, SO_2ArCH_3), 2.98 (1H, dd, *J* 15.7, 5.8, C(4)*H*H), 3.12 (1H, dd, *J* 15.7, 4.2, C(4)H*H*), 3.97 (1H, t, *J* 4.9, C(5)*H*), 7.02-7.03 (2H, m, Ar*H*), 7.14 (2H, d, *J* 8.2, Ar*H*), 7.19-7.23 (4H, m, Ar*H*), 7.26-7.47 (11H, m, Ar*H*).

Methyl 2-(4-methoxyphenyl)-6-oxo-5-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

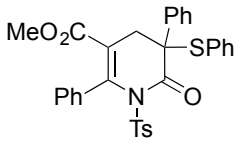


309

Following general procedure H, (phenylthio)phenyl acetic acid (147 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (15

mg, 0.08 mmol), ketimine **267** (112 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.3 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 10:90), the title compound as yellow oil (124 mg, 68%): ν_{max} (ATR)/cm^{-1} 1090 (S=O), 1321 (C-O), 1721 (C=O), 2889, 2999 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.06 (1H, d, *J* 15.6, C(4)*H*H), 3.44 (3H, s, CO_2CH_3), 3.50 (1H, d, *J* 15.6, C(4)H*H*), 3.78 (3H, s, $ArOCH_3$), 6.68 (2H, *J* 8.9, C(2)Ar(3,5)*H*), 6.88 (2H, d, *J* 8.4, Ar*H*), 7.18 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.21-7.28 (5H, m, Ar*H*), 7.31-7.36 (3H, m, Ar*H*), 7.39-7.40 (2H, m, Ar*H*), 7.54 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$); δ_C (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.8 (*C*(4)HH), 51.9 (CO_2CH_3), 55.3 ($ArOCH_3$), 63.3 (*C*(5)), 112.7 (C(2)Ar*C*(3,5)H), 118.6 (*C*(3)), 125.9 (C(2)Ar*C*(1)), 127.2 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (SO_2ArC(2,6)H), 128.9 (Ar*C*H), 129.1 (Ar*C*H), 129.2 (Ar*C*H), 129.6 (Ar*C*H), 130.4 (Ar*C*H), 130.8 (Ar*C*H), 135.6 (Ar*C*), 136.3 (Ar*C*), 136.5 (Ar*C*H), 145.1 (*C*(6)), 145.2 (SO_2ArC(1)), 160.1 (C(2)Ar*C*(4)), 166.0 (CO_2Me), 170.8 (*C*(6)); HRMS (NSI^+) $C_{27}H_{26}NO_6S_2$ ($[M+H]^+$) requires 524.1196 found 524.1191 (−1.0 ppm).

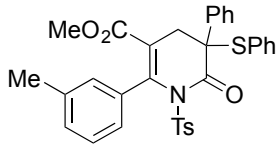
Methyl 6-oxo-2,5-diphenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



329

Following general procedure H, (phenylthio)phenyl acetic acid (195 mg, 0.8 mmol) and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) were added pivaloyl chloride (0.15 mL, 1.2 mmol) in CH_2Cl_2 (7 mL), DHPB **86** (15 mg, 0.08 mmol), ketimine **263** (137 mg, 0.4 mmol) and *i*-Pr_2NEt (70 μL, 0.4 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 10:90) and recrystallisation (Et_2O:isohexane), the title compound as white solid (174 mg, 77%): mp 152-154 °C; ν_{max} (ATR)/cm^{-1} 1048 (S=O), 1320 (C-O), 1719 (C=O), 2897, 3021 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 3.09 (1H, d, *J* 15.7, C(4)*H*H), 3.40 (3H, s, CO_2CH_3), 3.51 (1H, d, *J* 15.7, C(4)H*H*), 6.93 (2H, d, *J* 7.2, Ar*H*), 7.13-7.17 (4H, m, Ar*H*), 7.21-7.30 (6H, m, Ar*H*), 7.32-7.37 (3H, m, Ar*H*), 7.40-7.42 (2H, m, Ar*H*), 7.47 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.8 (*C*(4)HH), 51.9 (CO_2CH_3), 63.2 (*C*(5)), 119.4 (*C*(3)), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 128.7 (Ar*C*), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 129.1 (SO_2ArC(2,6)H), 129.2 (Ar*C*H), 129.5 (Ar*C*H), 129.7 (Ar*C*H), 130.5 (SO_2ArC(4)), 133.7 (Ar*C*), 135.6 (Ar*C*)), 136.2 (Ar*C*), 136.6 (Ar*C*H), 145.0 (*C*(2)), 145.1 (SO_2ArC(1)), 165.9 (CO_2Me), 170.8 (*C*(6)); HRMS (NSI^+) $C_{33}H_{29}NO_5S_2$ ($[M+H]^+$) requires 584.1560 found 584.1561 (+0.2 ppm).

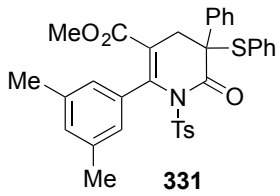
Methyl 6-oxo-5-phenyl-5-(phenylthio)-2-(3-tolyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



330

Following general procedure H, (phenylthio)phenyl acetic acid (403 mg, 1.65 mmol) and *i*-Pr_2NEt (0.0.43 mL, 2.46 mmol) were added pivaloyl chloride (0.30 mL, 2.46 mmol), DHPB **86** (31 mg, 0.16 mmol), ketimine **284** (294 mg, 0.82 mmol) and *i*-Pr_2NEt (0.14 mL, 0.82 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95), the title compound as 80% pure brown oil which was carried forward without further purification: (154 mg, 66%); ^1H NMR (400 MHz, $CDCl_3$) 2.12 (3H, s, C(2)ArC*H*$_3$) 2.43 (3H, s, SO_2ArC*H*$_3$), 3.11 (1H, d, *J* 15.6, C(4)*H*H), 3.42 (3H, s, CO_2C*H*$_3$), 3.51 (1H, d, *J* 15.7, C(4)H*H*), 6.55 (1H, s, C(2)Ar(2)*H*), 6.87 (1H, d, *J* 6.4, C(2)Ar(4)*H*), 7.08-7.10 (2H, m, Ar*H*), 7.17 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.24-7.48 (10H, m, Ar*H*), 7.50 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*).

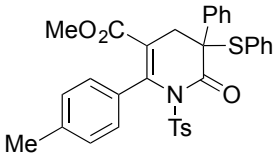
Methyl 2-(3,5-dimethylphenyl)-6-oxo-5-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



331

Following general procedure H, (phenylthio)phenyl acetic acid (293 mg, 1.2 mmol) and *i*-Pr_2NEt (0.31 mL, 1.8 mmol) were added pivaloyl chloride (0.22 mL, 1.8 mmol), DHPB **86** (23 mg, 0.12 mmol), ketimine **285** (223 mg, 0.6 mmol) and *i*-Pr_2NEt (0.11 mL, 0.6 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95), the title compound as 80% pure brown oil which was carried forward without further purification: ^1H NMR (400 MHz, $CDCl_3$) 2.15 (6H, s, C(2)Ar(3)C*H*$_3$ and C(2)Ar(5)C*H*$_3$), 2.46 (3H, s, SO_2ArC*H*$_3$), 3.12 (1H, d, *J* 15.6, C(4)*H*H), 3.44 (3H, s, CO_2C*H*$_3$), 3.49 (1H, d, *J* 15.6, C(4)H*H*), 6.52 (2H, s, Ar*H*), 6.91 (1H, s, Ar*H*), 7.20 (2H, d, *J* 8.0, Ar*H*), 7.23-7.32 (5H, m, Ar*H*), 7.34-7.41 (5H, Ar*H*), 7.53 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*).

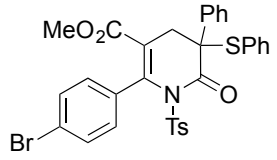
Methyl 6-oxo-5-phenyl-5-(phenylthio)-2-(4-tolyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



332

Following general procedure H, (phenylthio)phenyl acetic acid (195 mg, 0.8 mmol) and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) were added pivaloyl chloride (0.15 mL, 1.2 mmol), DHPB **86** (15 mg, 0.08 mmol), ketimine **286** (143 mg, 0.4 mmol) and *i*-Pr_2NEt (70 µL, 0.4 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (154 mg, 66%): mp 142-144 °C; ν_{max} (ATR)/cm^{-1} 1142 (S=O), 1342 (C-O), 1705 (C=O), 2924, 3032 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.32 (3H, s, C(2)ArC*H*$_3$), 2.45 (3H, s, SO_2ArC*H*$_3$), 3.06 (1H, d, *J* 15.7, C(4)*H*H), 3.43 (3H, s, CO_2C*H*$_3$), 3.49 (1H, d, *J* 15.6, C(4)H*H*), 6.84 (2H, Ar*H*), 6.97 (2H, d, *J* 7.9, Ar*H*), 7.16 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.22-7.26 (5H, m, Ar*H*), 7.31-7.36 (3H, m, Ar*H*), 7.38-7.40 (2H, m, Ar*H*), 7.52 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 C(2)Ar*C*H$_3$), 21.90 (SO_2Ar*C*H$_3$), 34.8 (*C*(4)HH), 51.9 (CO_2*C*H$_3$), 63.2 (*C*(5)), 118.9 (*C*(3)), 127.2 (Ar*C*H), 128.0 (SO_2Ar*C*(3,5)H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.6 (Ar*C*), 130.5 (Ar*C*), 135.6 (SO_2Ar*C*(4)), 136.3 (Ar*C*), 136.5 (Ar*C*), 139.0 (Ar*C*), 145.1 (SO_2Ar*C*(1)), 145.4 (*C*(2)), 166.0 (*C*O_2CH_3), 170.8 (*C*(6)); HRMS (NSI^+) $C_{33}H_{29}NO_5S_2$ ($[M+H]^+$) requires 584.1565 found 584.1540 (−1.1 ppm).

Methyl 2-(4-bromophenyl)-6-oxo-5-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

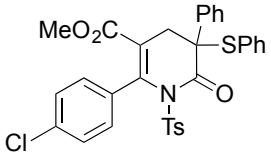


333

Following general procedure H, (phenylthio)phenyl acetic acid (147 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **287** (127 mg, 0.3 mmol) and *i*-Pr_2NEt (53 µL, 0.3 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (136 mg, 70%): mp 157-158 °C; ν_{max} (ATR)/cm^{-1} 1150 (S=O), 1377 (C-O), 1695 (C=O), 2951, 3065 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.46 (3H, s, SO_2ArC*H*$_3$), 3.06 (1H, d, *J* 15.8, C(4)*H*H), 3.45 (3H, s, CO_2C*H*$_3$), 3.51 (1H, d, *J* 15.8, C(4)H*H*), 6.79 (2H, d, *J* 8.2, Ar*H*), 7.19-7.25 (5H, m, Ar*H*), 7.27-7.29 (4H, m, Ar*H*), 7.32-7.35 (3H, m, Ar*H*), 7.37-7.39 (2H, m, Ar*H*), 7.52 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR

(100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.6 (*C*(4)HH), 52.1 (CO_2CH_3), 63.0 (*C*(5)), 119.9 (*C*(3)), 123.3 (C(2)Ar*C*(4)), 127.2 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (SO_2ArC(2,6)H), 129.8 (Ar*C*H), 130.3 (Ar*C*H), 130.5 (Ar*C*H), 131.1 (Ar*C*H), 132.7 (Ar*C*), 135.4 (Ar*C*), 136.1 (Ar*C*), 136.5 (Ar*C*H), 144.0 (SO_2ArC(1)), 145.4 (*C*(2)), 165.6 (*C*O_2Me), 170.5 (*C*(6)); HRMS (NSI^+) $C_{32}H_{27}{}^{79}BrNO_5S_2$ ($[M+H]^+$) requires 648.0509 found 648.0509 (+0.1 ppm).

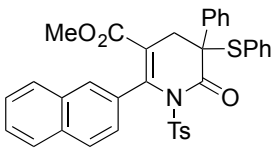
Methyl 2-(4-chlorophenyl)-6-oxo-5-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



334

Following general procedure H, (phenylthio)phenyl acetic acid (391 mg, 1.6 mmol) and *i*-Pr_2NEt (0.42 mL, 2.4 mmol) were added pivaloyl chloride (0.30 mL, 2.4 mmol), DHPB **86** (30 mg, 0.12 mmol), ketimine **288** (302 mg, 0.8 mmol) and *i*-Pr_2NEt (0.14 mL, 0.8 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (576 mg, 72%); mp 110-112 °C; ν_{max} (ATR)/cm^{-1} 1080 (S=O), 1343 (C-O), 1705 (C=O), 2901, 2986 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.46 (3H, s, SO_2ArCH_3), 3.06 (1H, d, *J* 15.8, C(4)*H*H), 3.44 (3H, s, CO_2CH_3), 3.51 (1H, d, *J* 15.8, C(4)H*H*), 6.86 (2H, d, *J* 8.1, Ar*H*), 7.13 (2H, d, *J* 8.7, Ar*H*), 7.19-7.27 (7H, m, Ar*H*), 7.31-7.39 (4H, m, Ar*H*), 7.53 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.7 (*C*(4)HH), 52.1 (CO_2CH_3), 63.0 (*C*(5)), 119.9 (*C*(3)), 127.16 (Ar*C*H), 127.6 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (SO_2ArC(2,6)H) 129.0 (Ar*C*H), 129.4 (Ar*C*H), 129.7 (Ar*C*H), 130.4 (Ar), 130.8 (Ar*C*H), 132.2 (C(2)Ar*C*(1)), 135.0 (C(5)Ar*C*(4)), 135.5 (SO_2ArC(4)), 136.1 (SAr*C*(1)), 136.5 (Ar*C*H), 144.0 (*C*(2)), 145.4 (SO_2ArC(1)), 165.6 (*C*O_2Me), 170.5 (*C*(6)); HRMS (NSI^+) $C_{32}H_{27}{}^{35}ClNO_6S_2$ ($[M+H]^+$) requires 604.1014 found 604.1013 (−0.1 ppm).

Methyl 2-(naphthalen-2-yl)-6-oxo-5-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

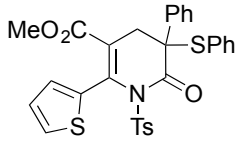


335

Following general procedure H, (phenylthio)phenyl acetic acid (147 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11

mg, 0.06 mmol), ketimine **290** (118 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.3 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95), the title compound as 80% pure brown oil which was carried forward without further purification; ^1H NMR (400 MHz, $CDCl_3$) 2.33 (3H, s, SO_2ArCH_3), 3.16 (1H, d, *J* 15.6, C(4)*H*H), 3.37 (3H, s, CO_2CH_3), 3.57 (1H, d, *J* 15.6, C(4)H*H*), 6.91 (2H, d, *J* 8.2, Ar*H*), 7.04 (1H, br. s, Ar*H*), 7.23-7.49 (16H, m, Ar*H*), 7.69 (1H, d, *J* 8.6, Ar*H*), 7.79 (1H, d, *J* 8.0, Ar*H*).

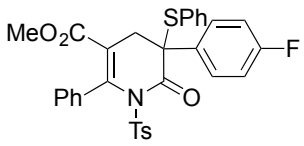
Methyl 6-oxo-5-phenyl-5-(phenylthio)-2-(thiophen-2-yl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



336

Following general procedure H, (phenylthio)phenyl acetic acid (147 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **291** (105 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.3 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:isohexane 5:95) and recrystallisation (Et_2O:isohexane), the title compound as white solid (119 mg, 69%): mp 134-136 °C; ν_{max} (ATR)/cm^{-1} 1087 (S=O), 1335 (C-O), 1697 (C=O), 2947, 3078 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.04 (1H, d, *J* 15.8, C(4)*H*H), 3.47 (1H, d, *J* 15.8, C(4)H*H*), 3.49 (3H, s, CO_2CH_3), 6.87 (2H, d, *J* 3.2, Ar*H*), 7.20-7.29 (9H, m, Ar*H*), 7.31-7.35 (2H, m, Ar*H*), 7.40 (2H, d, *J* 8.1, $SO_2Ar(2,6)H$); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2CH_3), 35.5 (*C*(4)HH), 52.2 (CO_2CH_3), 62.4 (*C*(3)), 122.0 (*C*(5)), 126.1 (Ar*C*H), 127.3 (Ar*C*H), 127.8 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.9 ($SO_2ArC(2,6)H$), 129.0 (Ar*C*H), 129.3 (Ar*C*H), 129.7 (Ar*C*), 130.4 (Ar*C*), 130.7 (Ar*C*H), 134.3 (Ar*C*), 135.6 (Ar*C*), 136.3 (Ar*C*), 136.6 (Ar*C*), 138.0 (Ar*C*), 145.2 ($SO_2C(1)$), 165.6 (CO_2CH_3), 170.4 (*C*(6)); HRMS (NSI^+) $C_{30}H_{26}NO_5S_3$ ($[M+H]^+$) requires 576.0968 found 576.0961 (−1.1 ppm).

Methyl 5-(4-fluorophenyl)-6-oxo-2-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

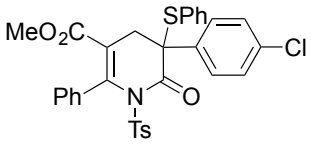


337

Following general procedure H, 2-(4-fluorophenyl)-2-(phenylthio)acetic acid (456 mg, 1.74 mmol) and *i*-Pr_2NEt (0.455 mL, 2.61 mmol) were added pivaloyl chloride (0.322 mL, 2.61 mmol), DHPB **86** (22 mg, 0.12 mmol), ketimine **263** (200 mg, 0.58 mmol) and *i*-Pr_2NEt (101

μL, 0.58 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc: Petrol 10:90), the title compound as white solid (170 mg, 50%): mp 122-125 °C; ν_{max} (ATR)/cm^{-1} 1144 (S=O), 1371 (C-O), 1697 (C=O), 2951, 3063 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 3.09 (1H, d, *J* 15.7, C(4)*H*H), 3.41 (3H, s, CO_2CH_3), 3.46 (1H, d, *J* 15.6, C(4)H*H*), 6.93-6.98 (4H, m, Ar*H*), 7.15-7.18 (4H, m, Ar*H*), 7.22-7.25 (2H, m, Ar*H*), 7.28-7.31 (1H, m, Ar*H*), 7.33-7.38 (5H, m, Ar*H*), 7.45 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.8 (*C*(4)HH), 52.0 (CO_2CH_3), 62.6 (*C*(5)), 115.8 (d, *J* 21.5, C(5)Ar*C*(3,5)H), 119.1 (*C*(3)), 127.3 (Ar*C*H), 129.0 (Ar*C*H), 129.0 (Ar*C*H), 129.1 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.5 (Ar*C*H), 129.9 (Ar*C*H), 130.2 (Ar*C*), 131.6 (d, *J* 3.4, C(5)Ar*C*(1)), 133.5 (Ar*C*), 136.0 (Ar*C*), 136.5 ($SO_2ArC(2,6)H$), 145.2 (Ar*C*), 145.2 (Ar*C*), 162.2 (d, *J* 249.2, C(5)Ar*C*(4)), 165.9 (*C*(6)), 170.6 (CO_2Me); HRMS (NSI$^+$) $C_{32}H_{26}FNO_5S_2Na$ ([M+Na]$^+$) requires 610.1129 found 610.1118 (−1.7 ppm).

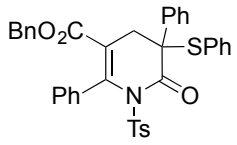
Methyl 5-(4-chlorophenyl)-6-oxo-2-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



338

Following general procedure H, 2-(4-chlorophenyl)-2-(phenylthio)acetic acid (167 mg, 0.6 mmol) and *i*-Pr_2NEt (0.16 mL, 0.9 mmol) were added pivaloyl chloride (0.11 mL, 0.9 mmol), DHPB **86** (11 mg, 0.06 mmol), ketimine **263** (105 mg, 0.3 mmol) and *i*-Pr_2NEt (53 μL, 0.3 mmol) for 30 min at rt gave, after chromatographic purification (EtOAc:Petrol 12:88) the title compound as colourless oil (128 mg, 71%): ν_{max} (ATR)/cm^{-1} 1150 (S=O), 1312 (C-O), 1722 (C=O), 2977, 3054 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3), 3.12 (1H, d, *J* 15.7, C(4)*H*H), 3.44-3.49 (4H, m, CO_2CH_3 and C(4)H*H*), 6.97 (2H, d, *J* 7.44, Ar*H*), 7.17-7.22 (4H, m, Ar*H*), 7.25-7.28 (4H, m, Ar*H*), 7.31-7.40 (6H, m, Ar*H*), 7.47 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.7 (*C*(4)HH), 52.0 (CO_2CH_3), 62.6 (*C*(5)), 119.0 (*C*(3)), 127.3 (Ar*C*H), 128.7 (Ar*C*H), 129.0 (Ar*C*H), 129.0 (Ar*C*H), 129.0 (Ar*C*H), 129.3 (Ar*C*H), 129.5 (Ar*C*H), 129.9 (Ar*C*H), 130.0 (Ar*C*H), 133.0 (Ar*C*), 133.4 (Ar*C*), 134.4 (Ar*C*), 134.6 (Ar*C*), 135.9 (Ar*C*), 136.5 ($SO_2ArC(2,6)H$), 145.2 (Ar*C*), 145.3 (Ar*C*), 165.8 (*C*(6)), 170.4 (CO_2Me); HRMS (NSI$^+$) $C_{32}H_{27}{}^{35}ClNO_5S_2$ ([M+H]$^+$) requires 604.1014 found 604.1013 (−0.1 ppm).

Benzyl 6-oxo-2,5-diphenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

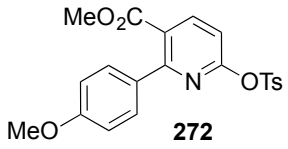


339

Following general procedure H, (phenylthio)phenyl acetic acid (147 mg, 0.6 mmol) and *i*-Pr_2NEt (157 µL, 0.9 mmol) were added pivaloyl chloride (111 µL, 0.9 mmol) in CH_2Cl_2 (5 mL), DHPB **86** (11 mg, 0.06 mmol), ketimine **263** (126 mg, 0.3 mmol) and *i*-Pr_2NEt (53 µL, 0.3 mmol) for 1 h at rt gave, after chromatographic purification (EtOAc:Petrol 12.5:87.5) and recrystallisation (Et_2O), the title compound as white solid (124 mg, 64%): mp 180-181 °C; ν_{max} (ATR)/cm^{-1} 1153 (S=O), 1728 (C=O), 2953, 3030 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 3.10 (1H, d, *J* 15.6, C(4)*H*H), 3.50 (1H, d, *J* 15.6, C(4)H*H*), 4.83 (2H, d, *J* 2.8, CO_2CH_2Ph), 6.86-6.93 (4H, m, Ar*H*), 7.06 (2H, t, *J* 7.8, Ar*H*), 7.14-7.28 (12H, m, Ar*H*), 7.32-7.35 (1H, m, Ar*H*), 7.39-7.40 (2H, m, Ar*H*), 7.46 (2H, d, *J* 8.3, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 34.7 (*C*(4)HH), 63.2 (*C*(5)), 66.7 (CO_2CH_2Ph), 119.6 (*C*(3)), 127.1 (Ar*C*H), 127.3 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 129.1 (Ar*C*H), 129.2 (Ar*C*H), 129.5 (Ar*C*H), 129.7 (Ar*C*H), 130.5 (Ar*C*), 133.6 (Ar*C*), 135.2 (Ar*C*), 135.4 (Ar*C*), 136.2 (Ar*C*), 136.7 (Ar*C*H), 145.1 (Ar*C*), 145.2 (Ar*C*), 165.3 (*C*(6)), 170.8 (CO_2Bn); HRMS (NSI^+) $C_{38}H_{35}N_2O_5S_2$ ($[M+NH_4]^+$), found 663.1983, requires 663.1982 (+0.2 ppm).

9.3.6 Oxidation-Sulfoxide Elimination/*N*- to *O*-Sulfonyl Transfer

Methyl 2-(4-methoxyphenyl)-6-(tosyloxy)nicotinate

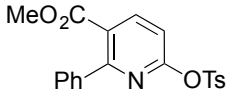


272

Following general procedure I, dihydropyridinone **268** (151 mg, 0.29 mmol) and Na_2CO_3 (1.19g, 11.3 mmol) in CH_2Cl_2 (6 mL), were added *m*-CPBA (71 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (105 mg, 88%): mp 105-107 °C; ν_{max} (ATR)/cm^{-1} 1172 (S=O), 1373 (C-O), 1713 (C=O), 2947, 2986 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3), 3.73 (3H, s, CO_2CH_3), 3.86 (3H, s, $ArOCH_3$), 6.89 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.04 (1H, d, *J* 8.3, C(5)*H*), 7.27-7.32 (4H, m, C(2)Ar(2,6)*H* and $SO_2Ar(3,5)H$), 7.92 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$), 8.09 (1H, d, *J* 8.3, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.7 (CO_2CH_3), 55.5 ($ArOCH_3$), 112.2 (*C*(5)H), 113.6 (C(2)Ar*C*(3,5)H), 124.9 (*C*(3)), 129.2 ($SO_2ArC(2,6)H$), 129.7 (C(2)Ar*C*(2,6)H), 130.5 ($SO_2ArC(3,5)H$), 130.7 (C(2)Ar*C*(1)), 134.1 ($SO_2ArC(4)$), 142.5 (C(4)*H*), 145.5

($SO_2ArC(1)$), 157.4 ($C(2)$), 157.7 (C(2)Ar$C(4)$), 160.8 ($C(6)$), 168.1 (CO_2CH_3); HRMS (NSI^+) $C_{21}H_{20}NO_6S$ ($[M+H]^+$) requires 414.1006 found 414.1001 (−2.1 ppm).

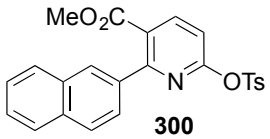
Methyl 2-phenyl-6-(tosyloxy)nicotinate



266

Following general procedure I, dihydropyridinone **264** (50 mg, 0.1 mmol) and Na_2CO_3 (413 mg, 3.9 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (25 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as colourless oil (36 mg, 93%); ν_{max} (ATR)/cm^{-1} 1172 (S=O), 1373 (C-O), 1728 (C=O), 2954, 3051 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.70 (3H, s, CO_2CH_3), 7.10 (1H, d, *J* 8.3 C(5)*H*), 7.29-7.33 (4H, m, C(2)Ar(3,5)*H* and SO_2Ar(3,5)*H*), 7.36-7.44 (3H, m, C(2)Ar(2,6)*H* and C(2)Ar(4)*H*), 7.91 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.15 (1H, d, *J* 8.3, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.6 (CO_2CH_3), 112.9 ($C(5)$H), 125.4 ($C(3)$), 128.1 (C(2)Ar$C(2,6)$H), 128.9 ($SO_2ArC(3,5)$H), 129.2 ($SO_2ArC(2,6)$H), 129.4 (C(2)Ar$C(4)$H), 129.7 (C(2)Ar$C(3,5)$H), 134.0 ($SO_2ArC(3,5)$H), 138.3 (C(2)Ar$C(1)$), 142.5 ($C(4)$H), 145.5 ($SO_2ArC(1)$), 157.5 ($C(2)$), 158.3 ($C(6)$), 167.7 (CO_2CH_3); HRMS (NSI^+) $C_{20}H_{18}NO_5S_1$ ($[M+H]^+$) requires 384.0900 found 384.0892 (−2.1 ppm).

Methyl 2-(naphthalen-2-yl)-6-(tosyloxy)nicotinate

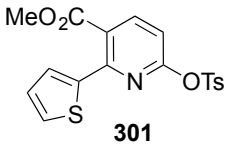


300

Following general procedure I, dihydropyridinone **296** (50 mg, 0.1 mmol) and Na_2CO_3 (413 mg, 0.39 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (25 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after column chromatography (EtOAc:isohexane 10:90), the title compound as colourless oil (36 mg, 90%): ν_{max} (ATR)/cm^{-1} 1172 (S=O), 1371 (C-O), 1732 (C=O), 2955, 3053 (C-H); ^1H NMR (300 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.67 (3H, s, CO_2CH_3), 7.14 (1H, d, *J* 8.3, C(5)*H*), 7.29 (2H, d, *J* 8.6, SO_2Ar(3,5)*H*), 7.42 (1H, dd, *J* 8.6, 1.8, C(2)Ar*H*), 7.50-7.57 (2H, m, C(2)Ar*H*), 7.81-7.89 (4H, m, C(2)Ar*H*), 7.94 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*), 8.20 (1H, d, *J* 8.3, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2CH_3), 52.7 (CO_2CH_3), 113.0 ($C(5)$H), 125.5 ($C(3)$), 126.3 (C(2)Ar*H*), 126.5 (C(2)Ar*H*), 127.1 (C(2)Ar*H*), 127.6 (C(2)Ar*H*), 127.9 (C(2)Ar*H*), 127.7 (C(2)Ar*H*), 127.9 (C(2)Ar*H*), 128.7 (C(2)Ar*H*), 128.8 (C(2)Ar*H*), 129.2

(SO_2Ar(2,6)H), 129.7 (SO_2Ar(3,6)H), 133.0 (C(2)Ar*C*(10)), 133.6 (C(2)Ar*C*(5)), 134.1 (SO_2Ar(4)), 135.7 (C(2)Ar*C*(2)), 142.6 (*C*(4)H), 145.5 (SO_2Ar*C*(1)), 157.7 (*C*(2)), 158.1 (*C*(6)), 167.8 (*C*O_2Me); HRMS (NSI^+) $C_{24}H_{20}NO_5S_1$ ($[M+H]^+$) requires 434.1057 found 434.1051 (−1.3 ppm).

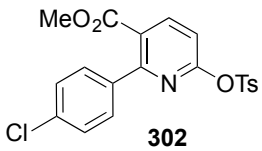
Methyl 2-(thiophen-2-yl)-6-(tosyloxy)nicotinate



301

Following general procedure I, dihydropyridinone **297** (50 mg, 0.10 mmol) and Na_2CO_3 (413 mg, 0.39 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (25 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (35 mg, 90%); mp 46-48 °C; ν_{max} (ATR)/cm^{-1} 1176 (S=O), 1365 (C-O), 1736 (C=O), 2899, 2964 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3), 3.87 (3H, s, CO_2CH_3), 7.01 (1H, d, *J* 8.3, C(5)*H*), 7.04 (1H, dd, *J* 5.1, 3.8, C(2)Ar(4)*H*), 7.32 (1H, dd, *J* 3.8, 1.0, C(2)Ar(3)*H*), 7.35 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.44 (1H, dd, *J* 5.1, 1.0, C(2)Ar(5)*H*), 7.96-7.99 (3H, m, C(4)*H* and SO_2Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2CH_3), 53.0 (CO_2CH_3), 112.8 (*C*(5)H), 124.1 (*C*(3)), 127.8 (C(2)Ar*C*(4)H), 128.9 (C(2)Ar*C*(3)H), 129.0 (SO_2Ar*C*(2,6)H), 129.6 (C(2)Ar*C*(5)H), 129.9 (SO_2Ar(3,5)H), 133.9 (SO_2Ar(4)), 141.0 (C(2)Ar*C*(2)), 142.1 (*C*(4)H), 145.5 (SO_2Ar*C*(1)), 150.2 (*C*(2)), 157.0 (*C*(6)), 167.9 (*C*O_2Me); HRMS (NSI^+) $C_{24}H_{22}NO_5S_3^+$ ($[M+H]^+$) requires 500.0660 found 500.0623 (−1.0 ppm).

Methyl 2-(4-chlorophenyl)-6-(tosyloxy)nicotinate

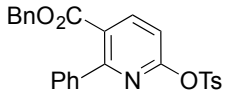


302

Following general procedure I, crude dihydropyridinone **298** (118 mg, 0.22 mmol) and Na_2CO_3 (922 mg, 8.70 mmol) in CH_2Cl_2 (4 mL), were added *m*-CPBA (56 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (68 mg, 54% over 2 steps): mp 117-119 °C; ν_{max} (ATR)/cm^{-1} 1172 (S=O), 1373 (C-O), 1728 (C=O), 2854, 2924 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3), 3.73 (3H, s, CO_2CH_3), 7.11 (1H, d, *J* 8.4, C(5)*H*), 7.25-7.31 (4H, m, SO_2Ar(3,5)*H* and C(2)Ar(3,5)*H*), 7.36 (2H, d, *J* 8.5, C(2)Ar(2,6)*H*), 7.90 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.17 (1H, d, *J* 8.4, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 22.2 (SO_2ArCH_3), 53.1 (CO_2CH_3), 113.5 (*C*(5)H), 125.4 (*C*(3)), 128.7 (C(2)Ar*C*(2,6)H), 129.5 (SO_2Ar*C*(2,6)H), 130.0 (C(2)Ar*C*(3,5)H), 130.7 (SO_2Ar*C*(3,5)H),

134.3 ($SO_2ArC(4)$), 136.0 (C(2)Ar*C*(4)), 137.3 (C(2)Ar*C*(1)), 143.1 (*C*(4)H), 146.0 ($SO_2ArC(1)$), 157.5 (*C*(2)), 158.0 (*C*(6)), 167.6 (CO_2Me); HRMS (NSI^+) $C_{20}H_{17}{}^{35}ClNO_5S_1$ ($[M+H]^+$) requires 418.0510 found 418.0502 (−2.0 ppm).

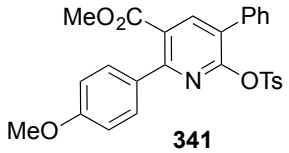
Benzyl 2-phenyl-6-(tosyloxy)nicotinate



303

Following general procedure I, dihydropyridinone **299** (91 mg, 0.16 mmol) and Na_2CO_3 (661 mg, 6.24 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (39 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (5 mL) for 1 h gave, after column chromatography (EtOAc:isohexane), the title compound as colourless oil (62 mg, 45% over 2 steps): ν_{max} (ATR)/cm^{-1} 1170 (S=O), 1373 (C-O), 1721 (C=O), 3032, 3062 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 5.13 (2H, s, CH_2), 7.02-7.05 (2H, Ar*H*), 7.10 (1H, d, *J* 8.4, C(5)*H*), 7.28-7.34 (9H, m, Ar*H*), 7.37 (1H, m, Ar*H*), 7.91 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$), 8.16 (1H, d, *J* 8.4, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_3ArCH_3), 67.7 (CH_2), 112.9 (*C*(5)H), 125.5 (*C*(3)), 128.1 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 129.0 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.7 (Ar*C*H), 134.0 (Ar*C*), 134.8 (Ar*C*), 138.3 (Ar*C*), 142.5 (Ar*C*), 145.5 ($SO_2ArC(1)$), 157.5 (*C*(2)), 158.4 (*C*(6)), 167.1 (CO_2Bn); HRMS (NSI^+) $C_{25}H_{20}NO_5S$ ($[M+H]^+$) requires 446.1062 found 446.1061 (−0.4 ppm).

Methyl 2-(4-methoxyphenyl)-5-phenyl-6-(tosyloxy)nicotinate

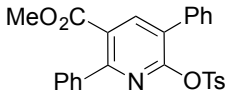


341

Following general procedure I, dihydropyridinone **309** (151 mg, 0.29 mmol) and Na_2CO_3 (1.19g, 11.3 mmol) in CH_2Cl_2 (6 mL), were added *m*-CPBA (71 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (105 mg, 88%); mp 148-151 °C; ν_{max} (ATR)/cm^{-1} 1170 (S=O), 1323(C-O), 1719 (C=O), 3010, 3026 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3) 2.43 (3H, s, SO_2ArCH_3), 3.76 (3H, s, CO_2CH_3), 3.89 (3H, s, $ArOCH_3$), 6.92 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.23 (2H, d, *J* 8.8, C(5)Ar(2,6)*H*), 7.37 (2H, d, *J* 8.09, $SO_2Ar(3,5)H$),, 7.40-7.48 (3H, m, C(5)Ar(3,5)*H* and C(5)Ar(4)*H*), 7.54-7.57 (2H, m, C(2)Ar(2,6)*H*), 7.85 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$), 8.13 C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 52.7 (CO_2CH_3), 55.5 ($ArOCH_3$), 113.5 (C(2)Ar*C*(3,5)H), 125.0 (*C*(3)), 125.6 (*C*(5)), 128.7 (C(5)Ar*C*(4)H), 128.8 (C(5)Ar*C*(3,5)H),

129.0 (SO_2ArC(2,6)H), 129.3 (C(2)Ar*C*(2,6)H), 129.5 (C(5)Ar*C*(2,6)H), 130.3 (C(5)Ar*C*(1)), 130.6 (SO_2ArC(3,5)H), 133.8 (C(5)Ar*C*(1)), 134.8 (SO_2ArC(4)), 142.8 (*C*(4)H), 145.1 (SO_2ArC(1)), 154.3 (*C*(2)), 155.7 (C(2)Ar*C*(4)), 160.7 (*C*(6)), 169.1 (CO_2Me); HRMS (NSI^+) $C_{27}H_{23}NO_6S^+$ ($[M+H]^+$) requires 490.1319 found 490.1316 (−0.6 ppm).

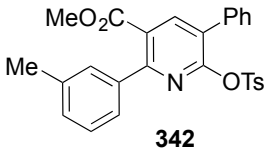
Methyl 2,5-diphenyl-6-(tosyloxy)nicotinate



340

Following general procedure I, dihydropyridinone **329** (147 mg, 0.25 mmol) and Na_2CO_3 (1.03g, 9.75 mmol) in CH_2Cl_2 (6 mL), were added *m*-CPBA (47 mg, 0.275 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (110 mg, 90%); mp 161-163 °C; ν_{max} (ATR)/cm^{-1} 1165 (S=O), 1366 (C-O), 1728 (C=O), 2947, 3055 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.42 (3H, s, SO_2ArCH_3), 3.72 (3H, s, CO_2CH_3), 7.21 (2H, d, *J* 8.1, ArC*H*), 7.39-7.50 (8H, m, ArC*H*), 7.55-7.59 (2H, m, ArC*H*), 7.85 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.18 (C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 52.6 (CO_2CH_3), 125.5 (*C*(3)), 126.3 (*C*(5)), 128.0 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 129.0 (SO_2ArC(2,6)H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.3 (Ar*C*H), 129.4 (Ar*C*H), 129.5 (Ar*C*H), 133.7 (Ar*C*), 134.8 (Ar*C*), 138.0 (Ar*C*), 142.8 (*C*(4)), 145.1 (Ar*C*), 154.5 (*C*(2)), 156.2 (*C*(6)), 167.7 (CO_2Me); HRMS (NSI^+) $C_{26}H_{21}NO_5S$ ($[M+H]^+$) requires 460.1213 found 460.1214 (−2.0 ppm).

Methyl 5-phenyl-2-(*m*-tolyl)-6-(tosyloxy)nicotinate

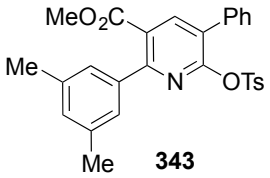


342

Following general procedure I, crude dihydropyridinone **330** (314 mg, 0.54 mmol) and Na_2CO_3 (2.24 g, 21.1 mmol) in CH_2Cl_2 (12 mL), were added *m*-CPBA (132 mg, 0.59 mmol) in CH_2Cl_2 (6 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (217 mg, 56% over 2 steps): mp 144-145 °C; ν_{max} (ATR)/cm^{-1} 1167 (S=O), 1369 (C-O), 1727 (C=O), 2920, 3051 (C-H); ^1H NMR (400 MHz, $CDCl_3$) 2.41 (3H, s, SO_2Ar(3,5)*H*), 2.43 (3H, s, C(2)ArCH_3), 3.72 (3H, s, CO_2CH_3), 7.17-7.30 (6H, m, C(2)Ar(2)*H* and C(2)Ar(4)*H* and C(2)Ar(5)*H* and C(2)Ar(6)*H* and SO_2Ar(3,5)*H*), 7.41-7.50 (3H, m, C(5)Ar(3,5)*H* and C(5)Ar(4)*H*), 7.56-7.59 (2H, m, C(5)Ar(2,6)*H*), 7.85 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*), 8.16 (1H, s,

C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 (SO_2ArCH_3), 21.9 (C(2)ArCH_3), 52.7 (CO_2CH_3), 125.7 (Ar*C*), 126.2 (C(2)Ar*C*(4)H), 126.4 (Ar*C*), 127.9 (C(2)Ar*C*(6)H), 128.8 (C(5)Ar*C*(3,5)H), 129.2 (SO_2ArC(2,6)H), 129.3 (C(5)Ar*C*(2,6)H), 129.5 (SO_2ArC(3,5)H), 129.6 (C(2)Ar(5)H), 130.2 (C(2)Ar(2)H), 133.8 (Ar*C*), 134.9 (Ar*C*), 137.7 (Ar*C*), 137.9 (Ar*C*), 142.7 (*C*(4)H), 145.0 (SO_2ArC(1)), 154.5 (*C*(2)), 156.3 (*C*(6)), 167.9 (CO_2Me); HRMS (NSI$^+$) $C_{27}H_{24}NO_5S$ ([M+H]$^+$) requires 474.1370 found 474.1359 (−2.3 ppm).

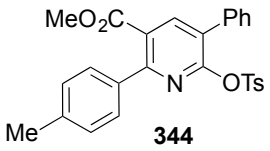
Methyl 2-(3,5-dimethylphenyl)-5-phenyl-6-(tosyloxy)nicotinate



343

Following general procedure I, crude dihydropyridinone **331** (179 mg, 0.3 mmol) and Na_2CO_3 (1.36 g, 12.8 mmol) in CH_2Cl_2 (6 mL), were added *m*-CPBA (74 mg, 0.33 mmol) in CH_2Cl_2 (4 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (129 mg, 44% over 2 steps): mp 135-137 °C; ν_{max} (ATR)/cm^{-1} 1163 (S=O), 1356 (C-O), 1727 (C=O), 2952, 3015 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.37 (6H, s, C(2)Ar(3)CH_3 and C(2)Ar(5)CH_3), 2.45 (3H, s, SO_2Ar(CH_3), 3.74 (3H, s, CO_2CH_3), 7.00 (2H, s, C(2)Ar(2,6)*H*), 7.08 (1H, s, C(2)Ar(4)*H*), 7.26 (2H, m, SO_2Ar(3,5)*H*), 7.44-7.51 (3H, m, Ar*H*), 7.58-7.60 (2H, m, C(5)Ar(2,6)*H*), 7.87 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.15 (1H, s, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.5 (C(2)ArCH_3), 21.5 (C(2)ArCH_3), 21.9 (SO_2ArCH_3), 52.6 (CO_2CH_3), 125.8 (Ar*C*), 126.4 (Ar*C*), 126.8 (C(2)Ar*C*(2,6)H), 128.8 (C(5)Ar*C*(4)H), 128.8 (C(5)Ar*C*(3,5)H), 129.1 (SO_2ArC(2,6)H), 129.3 (C(5)Ar*C*(2,6)H), 129.5 (SO_2ArC(3,5)H), 131.1 (C(2)Ar*C*(4)H), 133.8 (Ar*C*), 135.0 (Ar*C*), 137.5 (Ar*C*), 137.8 (Ar*C*), 142.6 (*C*(4)H), 144.9 (SO_2ArC(1)), 154.4 (*C*(2)), 156.4 (*C*(6)), 168.1 (CO_2Me); HRMS (NSI$^+$) $C_{19}H_{20}NO_4S$ ([M+H]$^+$) requires 358.1108 found 358.1103 (−1.3 ppm).

Methyl 5-phenyl-2-(p-tolyl)-6-(tosyloxy)nicotinate

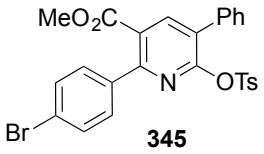


344

Following general procedure I, dihydropyridinone **332** (108 mg, 0.19 mmol) and Na_2CO_3 (785 mg, 7.41 mmol) in CH_2Cl_2 (4 mL), were added *m*-CPBA (47 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (84 mg, 93%):

mp 152-155 °C; ν_{max} (ATR)/cm^{-1} 1175 (S=O), 1373 (C-O), 1711 (C=O), 2949, 3046 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.43 (6H, d, *J* 2.1, SO_2ArCH_3 and C(2)ArCH_3), 3.74 (3H, s, CO_2CH_3), 7.19-7.24 (4H, m, SO_2Ar(3,5)*H* and C(2)Ar(3,5)*H*), 7.30 (2H, d, *J* 8.1, C(2)Ar(2,6)*H*), 7.42-7.49 (3H, m, C(5)Ar(3,5)*H*) and C(5)Ar(4)*H*), 7.55-7.57 (2H, m, C(5)Ar(2,6)*H*), 7.85 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.15 (1H, s, C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.6 (C(2)ArCH_3), 21.9 (SO_2ArCH_3), 52.7 (CO_2CH_3), 125.4 (Ar*C*), 126.0 (Ar*C*), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.5 (Ar*C*H), 133.8 (Ar*C*), 134.9 (Ar*C*), 135.1 (Ar*C*), 139.5 (Ar*C*), 142.8 (*C*(4)H), 145.1 (SO_2ArC(1)), 154.5 (*C*(2)), 156.2 (*C*(6)), 168.0 (CO_2Me); HRMS (NSI$^+$) $C_{27}H_{24}NO_5S$ ([M+H]$^+$) requires 474.1370 found 474.1370 (+0.1 ppm).

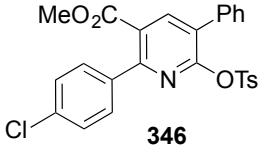
Methyl 2-(4-bromophenyl)-5-phenyl-6-(tosyloxy)nicotinate



345

Following general procedure I, dihydropyridinone **333** (50 mg, 0.08 mmol) and Na_2CO_3 (318 mg, 3.00 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (19 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O), the title compound as white solid (39 mg, 94%); mp 160-161 °C ; ν_{max} (ATR)/cm^{-1} 1165 (S=O), 1366 (C-O), 1744 (C=O), 2955, 3055 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, SO_2ArCH_3), 3.75 (3H, s, CO_2CH_3), 7.23 (2H, d, *J* 8.1, C(2)Ar(3,5)*H*), 7.28 (2H, d, *J* 8.5, SO_2Ar(3,5)*H*), 7.42-7.49 (3H, m, C(5)Ar(3,5)*H* and C(5)Ar(4)*H*), 7.53-7.57 (4H, m, C(5)Ar(2,6)*H* and C(2)Ar(2,6)*H*), 7.82 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.20 (C(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.8 (CO_2CH_3), 124.0 (Ar*C*), 125.2 (Ar*C*), 126.7 (Ar*C*), 128.9 (C(5)Ar*C*(3,5)H), 128.9 (C(5)Ar*C*(4)H), 129.1 (SO_2ArC(2,6)H), 129.3 (C(2)Ar*C*(2,6)H), 129.5 (C(2)Ar*C*(3,5)H), 130.8 (SO_2ArC(3,5)H), 131.3 (C(5)Ar*C*(2,6)H), 133.5 (Ar*C*), 134.8 (Ar*C*), 136.9 (Ar*C*), 143.1 (*C*(4)H), 145.3 (SO_2ArC(1)), 154.6 (*C*(2)), 155.2 (*C*(6)), 167.3 (CO_2Me); HRMS (NSI$^+$) $C_{26}H_{21}{}^{79}BrNO_5S$ ([M+H]$^+$) requires 538.0318 found 538.0311 (−1.4 ppm).

Methyl 2-(4-chlorophenyl)-5-phenyl-6-(tosyloxy)nicotinate

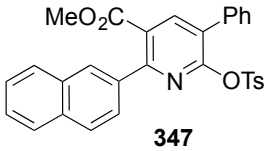


346

Following general procedure I, crude dihydropyridinone **334** (179 mg, 0.3 mmol) and Na_2CO_3 (1.36 g, 12.8 mmol) in CH_2Cl_2 (6 mL), were added *m*-CPBA (74 mg, 0.33 mmol) in CH_2Cl_2 (4

mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (129 mg, 44% over 2 steps): mp 145-147; °C ν_{max} (ATR)/cm^{-1} 1161 (S=O), 1377 (C-O), 1726 (C=O), 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 3.75 (3H, s, CO_2CH_3), 7.23 (2H, d, *J* 8.1, $SO_2Ar(3,5)H$), 7.33-7.40 (4H, m, C(2)Ar(3,5)*H* and C(2)Ar(2,6)*H*), 7.43-7.49 (3H, m, C(5)Ar(3,5)*H* and C(5)Ar(4)*H*), 7.55-7.57 (2H, m, C(5)ArC(2,6)*H*), 7.82 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$), 8.20 (1H, C(4)*H*); ^{1}H NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.8 (CO_2CH_3), 125.2 (Ar*C*), 126.7 (Ar*C*), 128.3 (C(2)Ar*C*(2,6)H), 128.9 (C(5)Ar*C*(3,5)H), 128.9 (C(5)Ar*C*(4)H), 129.1 (SO_2ArC(2,6)H), 129.3 (C(5)Ar*C*(2,6)H), 129.5 (SO_2ArC(3,5)H), 130.5 (C(2)Ar*C*(3,5)H), 133.5 (Ar*C*), 134.8 (Ar*C*), 135.6 (Ar*C*), 136.5 (Ar*C*), 143.1 (*C*(4)H), 145.3 (SO_2ArC(1)), 154.6 (*C*(2)), 155.1 (*C*(6)), 167.3 (CO_2Me); HRMS (NSI$^+$) $C_{26}H_{21}{}^{35}ClNO_5S$ ([M+H]$^+$) requires 494.0823 found 494.0818 (−1.1 ppm).

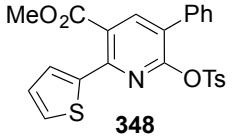
Methyl 2-(naphthalen-2-yl)-5-phenyl-6-(tosyloxy)nicotinate



347

Following general procedure I, dihydropyridinone **335** (121 mg, 0.20 mmol) and Na_2CO_3 (980 mg, 9.24 mmol) in CH_2Cl_2 (5 mL), were added *m*-CPBA (58 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after column chromatography (EtOAc:isohexane, 5:95), the title compound as white solid (35 mg, 90%): mp 149-151 °C; ν_{max} (ATR)/cm^{-1} 1175 (S=O), 1371 (C-O), 1732 (C=O), 3049, 3065 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.41 (3H, s, SO_2ArCH_3), 3.70 (3H, s, CO_2CH_3), 7.20 (2H, d, *J* 8.2, $SO_2Ar(3,5)H$), 7.42-7.62 (8H, m, Ar*H*), 7.86-7.92 (6H, m, Ar*H*), 8.23 (1H, s, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 52.7 (CO_2CH_3), 125.7 (*C*(3)), 126.4 (Ar*C*H), 126.5 (Ar*C*H), 126.5 (Ar*C*H), 127.1 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 129.2 (Ar*C*H), 129.4 (Ar*C*H), 129.5 (Ar*C*H), 133.1 (Ar*C*), 133.7 (Ar*C*), 133.7 (Ar*C*), 135.0 (Ar*C*), 135.4 (Ar*C*), 143.0 (*C*(4)H), 145.1 (Ar*C*), 154.7 (Ar*C*), 156.1 (*C*(6)), 167.8 (CO_2Me); HRMS (NSI$^+$) $C_{30}H_{24}NO_5S^+$ ([M+H]$^+$) requires 510.1370 found 510.1362 (−1.5 ppm).

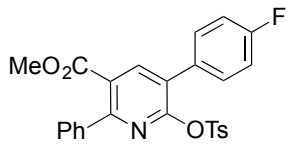
Methyl 5-phenyl-2-(thiophen-2-yl)-6-(tosyloxy)nicotinate



348

Following general procedure I, dihydropyridinone **336** (50 mg, 0.09 mmol) and Na_2CO_3 (372 mg, 3.51 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (22 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (37 mg, 88%): mp 122-123 °C; ν_{max} (ATR)/cm^{-1} 1167 (S=O), 1373 (C-O), 1732 (C=O), 2949, 3117 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.45 (3H, s, SO_2ArCH_3), 3.90 (3H, s, CO_2CH_3), 7.08 (1H, t, *J* 4.2, C(1)Ar(4)*H*), 7.31 (2H, d, *J* 7.8, SO_2Ar(3,5)*H*), 7.37-7.47 (5H, m, C(5)Ar(4)*H*) and C(5)Ar(3,5)*H* and C(1)Ar(3)*H* and C(1)Ar(5)*H*), 7.56 (2H, d, *J* 7.3, C(5)Ar(2,6)*H*), 7.93 (2H, d, *J* 7.8 SO_2Ar(2,6)*H*), 8.04 (1H, s, C(3)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 53.0 (CO_2CH_3), 124.3 (Ar*C*), 126.2 (Ar*C*), 127.8 (C(1)Ar*C*(4)H), 128.8 (SO_2ArC(2,6)H), 128.8 (C(1)Ar*C*(3)H) 128.9 (C(1)Ar*C*(5)H), 129.0 (C(5)Ar*C*(4)H), 129.3 (C(5)Ar*C*(3,5)H), 129.5 (C(5)Ar*C*(2,6)H), 129.7 (SO_2ArC(3,5)H), 133.7 (Ar*C*), 134.6 (Ar*C*), 140.8 (Ar*C*), 142.4 (*C*(4)H), 145.2 (SO_2ArC(1)), 148.4 (*C*(2)), 153.9 (*C*(6)), 167.8 (CO_2Me); HRMS (NSI$^+$) $C_{24}H_{20}NO_5S_2$ ([M+H]$^+$) requires 466.0777 found 466.0772 (−1.2 ppm).

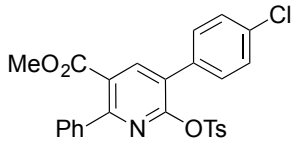
Methyl 5-(4-fluorophenyl)-2-phenyl-6-(tosyloxy)nicotinate



349

Following general procedure I, dihydropyridinone **337** (105 mg, 0.179 mmol) and Na_2CO_3 (737 mg, 6.98 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (44 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O), the title compound as white solid (80 mg, 90%): mp 188-190 °C; ν_{max} (ATR)/cm^{-1} 1171 (S=O), 1371 (C-O), 1721 (C=O), 3055 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 3.72 (3H, s, CO_2CH_3), 7.14-7.19 (2H, m, C(5)Ar(3,5)*H*), 7.23 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.38-7.45 (5H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H* and C(2)Ar(2,6)*H*), 7.53-7.57 (2H, m, C(5)Ar(2,6)*H*), 7.85 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.15 (1H, s, C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.7 (CO_2CH_3), 116.0 (d, *J* 21.7, C(5)Ar*C*(3,5)H), 125.4 (*C*(3)), 125.5 (*C*(5)), 128.1 (C(2)Ar*C*(3,5)H), 129.1 (SO_2ArC(2,6)H), 129.2 (C(2)Ar*C*(2,6)H), 129.4 (C(2)Ar*C*(4)H), 129.5 (SO_2ArC(3,5)H), 129.7 (d, *J* 3.3, C(5)Ar*C*(1)), 131.2 (d, *J* 8.4, C(5)Ar*C*(2,6)H), 134.7 (Ar*C*), 137.9 (Ar*C*), 142.7 (*C*(4)), 145.3 (SO_2ArC(1)), 154.4 (*C*(2)), 156.4 (*C*(6)), 163.1 (d, *J* 249.0, C(5)Ar*C*(4)), 167.7 (CO_2Me); ^{19}F NMR (376 MHz, $CDCl_3$) 112.6 (C(5)Ar*F*). HRMS (NSI$^+$) $C_{26}H_{21}FNO_5S$ ([M+H]$^+$) requires 478.1119 found 478.1114 (−1.0 ppm).

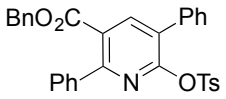
Methyl 5-(4-chlorophenyl)-2-phenyl-6-(tosyloxy)nicotinate



350

Following general procedure I, dihydropyridinone **338** (110 mg, 0.18 mmol) and Na_2CO_3 (636 mg, 6.00 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (45 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O), the title compound as white solid (80 mg, 90%): mp 194-196 °C; ν_{max} (ATR)/cm^{-1} 1176 (S=O), 1435 (C-O), 1697 (C=O), 2789 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.43 (3H, s, SO_2ArCH_3), 3.72 (3H, s, CO_2CH_3), 7.22 (2H, d, *J* 8.2, $SO_2Ar(3,5)H$), 7.39-7.51 (9H, m, Ar*H*), 7.84 (2H, d, *J* 8.2, $SO_2Ar(2,6)H$), 8.15 (1H, s, C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 52.7 (CO_2CH_3), 125.2 (*C*(3)), 125.6 (*C*(5)), 128.1 (Ar*C*H), 129.1 ($SO_2ArC(2,6)H$), 129.1 (Ar*C*H), 129.1 (Ar*C*H), 129.5 (Ar*C*H), 129.5 ($SO_2ArC(3,5)H$), 130.6 (Ar*C*H), 132.1 (Ar*C*), 134.6 (Ar*C*), 135.1 (Ar*C*), 137.8 (Ar*C*), 142.6 (Ar*C*), 145.3 ($SO_2ArC(1)$), 154.4 (*C*(2)), 156.6 (*C*(6)), 167. 6 (CO_2Me); HRMS (NSI$^+$) $C_{26}H_{21}{}^{35}ClNO_5S$ ([M+H]$^+$) requires 494.0823 found 494.0812 (−2.3 ppm).

Benzyl 2,5-diphenyl-6-(tosyloxy)nicotinate

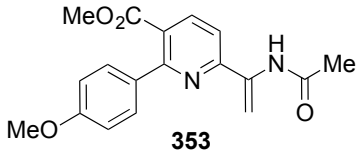


351

Following general procedure I, dihydropyridinone **339** (64 mg, 0.099 mmol) and Na_2CO_3 (409 mg, 3.86 mmol) in CH_2Cl_2 (3 mL), were added *m*-CPBA (25 mg, 0.109 mmol) in CH_2Cl_2 (2 mL) for 30 min to give intermediate pyridone. Crude mixture heated at 80 °C in THF (10 mL) for 1 h gave, after recrystallisation (Et_2O:isohexane), the title compound as white solid (48 mg, 90%); mp 122-124 °C; ν_{max} (ATR)/cm^{-1} 1166 (S=O), 1368 (C-O), 1724 (C=O), 3032, 3063 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.44 (3H, s, SO_2ArCH_3), 5.18 (2H, s, CO_2CH_2Ph), 7.06-7.08 (2H, m, Ar*H*), 7.23 (2H, d, *J* 8.1, Ar*H*), 7.30-7.51 (11H, m, Ar*H*), 7.57-7.59 (2H, m, Ar*H*), 7.86 (2H, d, *J* 8.3, $SO_2Ar(2,6)H$), 8.20 (1H, s, C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (SO_2ArCH_3), 67.7 (CO_2CH_2Ph), 125.7 (*C*(3)), 126.3 (*C*(5)), 128.1 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (Ar*C*H), 129.3 (Ar*C*H), 129.5 (Ar*C*H), 133.7 (Ar*C*), 134.7 (Ar*C*), 134.8 (Ar*C*), 138.0 (Ar*C*), 142.7 (*C*(4)H), 145.1 ($SO_2ArC(1)$), 154.5 (*C*(2)), 156.2 (*C*(6)), 167.2 (CO_2Bn); HRMS (NSI$^+$) $C_{32}H_{26}NO_5S$ ([M+H]$^+$) requires 536.1526 found 536.1519 (−1.3 ppm).

9.3.7 Derivatisations

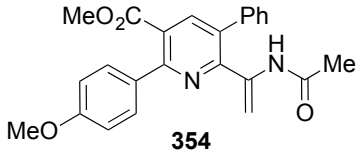
Methyl 6-(1-acetamidovinyl)-2-(4-methoxyphenyl)nicotinate



353

Following the procedure of Gøgsig and co-workers[170] A solution of **270** (100 mg, 0.24 mmol), *N*-vinylacetamide (61 mg, 0.72 mmol), *N*-methyldicyclohexylamine (206 µL, 0.96 mmol), DPPF (7 mg, 0.012 mmol) and [Pd(dba)$_2$] (7 mg, 0.012 mmol) were stirred in 1,4-dioxane (2 mL) in a screw top vial at 100 °C for 16 h. Once cooled, the reaction was filtered through celite (eluent CH_2Cl_2) and concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 25:75) gave the title compound as yellow oil (56 mg, 72%); ν_{max} (ATR)/cm^{-1} 1253, 1429, 1728 (C=O), 2839, 2951 (C-H), 3327 (N-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.18 (3H, s, C*H*$_3$), 3.75 (3H, s, CO_2CH_3), 3.88 (3H, s, ArOC*H*$_3$), 5.65 (1H, s, =C*H*H), 6.61 (1H, s, =CH*H*), 7.00 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.52 (2H, d, *J* 8.8, C(2)Ar(2,6)*H*), 7.72 (1H, d, *J* 8.3, C(5)*H*), 8.10 (1H, d, *J* 8.30, C(4)*H*), 9.27 (1H, br. s, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 25.2 (*C*H$_3$), 52.6 (CO_2CH_3), 55.5 (ArO*C*H$_3$), 101.3 (=*C*HH), 113.8 (C(2)Ar*C*(3,5)H), 116.3 (*C*(5)H), 125.6 (*C*(3)), 130.2 (C(2)Ar*C*(2,6)H), 132.1 (C(2)Ar*C*(1)), 137.0 (*C*=CHH), 139.3 (*C*(4)H), 153.3 (*C*(2)), 156.8 (*C*(6)), 160.6 (C(2)Ar*C*(4)), 168.4 (NH*C*OMe), 169.3 (CO_2Me); HRMS (NSI$^+$) $C_{18}H_{19}N_2O_4$ ([M+H]$^+$) requires 327.1339 found 327.1342 (+0.8 ppm).

Methyl 6-(1-acetamidovinyl)-2-(4-methoxyphenyl)-5-phenylnicotinate

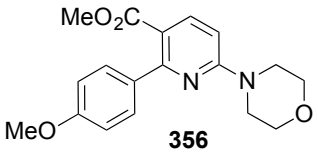


354

Following the procedure of Gøgsig and co-workers[170] A solution of **341** (100 mg, 0.20 mmol), *N*-vinylacetamide (68 mg, 0.80 mmol), *N*-methyldicyclohexylamine (171 µL, 0.80 mmol), DPPF (6 mg, 0.010 mmol) and [Pd(dba)$_2$] (6 mg, 0.010 mmol) were stirred in 1,4-dioxane (2 mL) in a screw top vial at 100 °C for 16 h. Once cooled, the reaction was filtered through celite (eluent CH_2Cl_2) and concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 30:70) gave the title compound as yellow oil (55 mg, 69%); ν_{max} (ATR)/cm^{-1} 1246, 1425, 1717 (C=O), 2837, 2949 (C-H), 3296 (N-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.07 (3H, s, C*H*$_3$), 3.76 (3H, s, CO_2CH_3), 3.89 (3H, s, ArOC*H*$_3$), 4.84 (1H, s, =C*H*H), 6.27 (1H, s, =CH*H*), 7.01 (2H, d, *J* 8.9), 7.36-7.46 (4H, m, C(5)Ar(2,6)*H*, C(5)Ar(3,5)*H* and C(5)Ar(4)*H*), 7.58 (2H, d, *J* 8.9, C(2)Ar*C*(2,6)H), 8.03 (1H, s, C(4)*H*), 8.55 (1H, br. s, N*H*); ^{13}C NMR (100

MHz, $CDCl_3$) 25.1 (*C*H_3), 52.6 (CO_2*C*H_3), 55.5 (ArO*C*H_3), 108.1 (=*C*HH), 113.9 (C(2)Ar*C*(3,5)H), 125.1 (*C*(3)), 128.2 (C(5)Ar*C*(4)H), 128.8 (C(5)Ar*C*(3,5)H), 129.1 (C(5)Ar*C*(2,6)H), 130.3 (C(2)Ar*C*(2,6)H), 131.7 (C(2)Ar*C*(1)), 133.5 (*C*(5)), 136.7 (C(5)Ar*C*(1)), 139.0 (*C*=CHH), 141.9 (*C*(4)H), 152.4 (*C*(2)), 155.4 (*C*(6)), 160.6 (C(2)Ar*C*(4)), 168.2 (NH*C*OMe), 169.2 (CO_2Me); HRMS (NSI^+) $C_{24}H_{23}N_2O_4$ ($[M+H]^+$) requires 403.1652 found 403.1655 (+0.7 ppm).

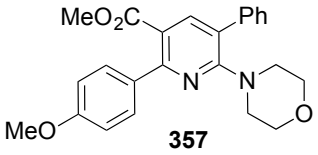
Methyl 2-(4-methoxyphenyl)-6-morpholinonicotinate



356

Following the procedure by Volochnyuk *et al*.[178] A solution of **341** (100 mg, 0.24 mmol), morpholine (0.207 mL, 2.4 mmol), Et_3N (67 µL, 0.48 mmol) were stirred in toluene (2 mL) in a screw top vial at 120 °C for 16 h. Once cooled, the reaction was concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 25:75) gave the title compound as colourless oil (62 mg, 80%); ν_{max} (ATR)/cm^{-1} 1111, 1225, 1587, 1722, 2883, 2949 (C-H) ^{1}H NMR (500 MHz, $CDCl_3$) 3.65-3.68 (7H, m, CO_2CH_3 and 2×O*CH*$_2$), 3.79-3.81 (4H, m, 2×NC*H*$_2$), 3.85 (3H, s, ArO*CH*$_3$), 6.52 (1H, d, *J* 8.9, C(5)*H*), 6.93 (2H, d, *J* 8.7, C(2)Ar(3,5)*H*), 7.48 (2H, d, *J* 8.7, C(2)Ar(2,6)*H*), 8.00 (1H, d, *J* 8.9, C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 45.0 (O*C*H$_2$), 51.8 (CO_2CH_3), 55.4 (ArO*C*H_3), 66.8 (N*C*H$_2$), 103.3 (*C*(5)H), 113.2 (C(2)Ar*C*(3,5)H), 114.6 (*C*(3)), 130.3 (C(2)Ar*C*(2,6)H), 133.6 (C(2)Ar*C*(1)), 140.7 (*C*(5)H), 159.0 (*C*(2)), 159.1 (*C*(6)), 160.0 (C(2)Ar*C*(4)), 168.5 (CO_2Me); HRMS (NSI^+) $C_{18}H_{21}N_2O_4^+$ ($[M+H]^+$) requires 329.1496 found 329.1497 (+0.4 ppm).

Methyl 2-(4-methoxyphenyl)-6-morpholino-5-phenylnicotinate

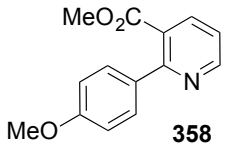


357

Following the procedure by Volochnyuk *et al*.[178] A solution of **341** (100 mg, 0.24 mmol), morpholine (172 µL, 2.00 mmol), Et_3N (56 µL, 0.40 mmol) were stirred in toluene (2 mL) in a screw top vial at 120 °C for 16 h. Once cooled, the reaction was concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 15:85) gave the title compound as colourless oil (59 mg, 73%); ν_{max} (ATR)/cm^{-1} 1107, 1230, 1624, 1722, 2882, 2951 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.27-3.29 (4H, m, O*CH*$_2$), 3.61-3.64 (4H, m, N*CH*$_2$), 3.71 (3H, s, CO_2CH_3), 3.87 (3H, s, ArO*CH*$_3$), 6.96 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.31-7.35 (1H, m,

C(5)Ar(4)*H*), 7.41-7.45 (2H, m, C(5)Ar(3,5)*H*), 7.56-7.59 (4H, m, C(5)Ar(2,6)*H* and C(2)Ar(2,6)*H*), 7.95 (1H, s, C(4)*H*)); ^{13}C NMR (125 MHz, $CDCl_3$) 48.8 (OCH_2), 52.0 (CO_2CH_3), 55.4 ($ArOCH_3$), 66.7 (NCH_3), 113.4 (C(2)Ar*C*(3,5)H), 117.6 (*C*(3)), 122.3 (C(2)Ar*C*(1)), 127.7 (C(5)Ar*C*(2,6)H), 127.7 (C(5)Ar*C*(5)H), 129.1 (C(5)*C*(3,5)H), 130.5 (C(2)Ar*C*(2,6)H), 132.8 (*C*(5)), 139.4 (C(5)Ar*C*(1)), 142.6 (*C*(4)H), 156.2 (*C*(2)), 158.9 (C(2)Ar*C*(4)), 160.3 (*C*(6)), 168.8 (CO_2Me); HRMS (NSI^+) $C_{24}H_{25}N_2O_4$ ($[M+H]^+$) requires 405.1809 found 405.1801 (−1.9 ppm).

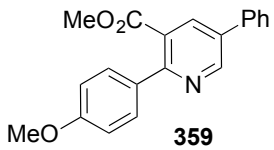
Methyl 2-(4-methoxyphenyl)nicotinate



358

Following the procedure from Yoshida *et al*.[80] To a solution of **270** (50 mg, 0.12 mmol), $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), DPPP (2.5 mg, 0.006 mmol), and Et_3N (84 µL, 0.6 mmol), in DMF (1 mL) was added formic acid (14 µL, 0.36 mmol). The reaction was heated in a screw top vial for 16 h at 100 °C. Once cooled, the reaction mixture was quenched with brine and extracted with EtOAc (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatographic purification (EtOAc:Petrol 15:85) gave the title compound as colourless oil (23 mg, 78%); ν_{max} (ATR)/cm^{-1} 1253, 1429 (C-O), 1728 (C=O), 2837, 2951 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.73 (3H, s, CO_2CH_3), 3.85 (3H, s, $ArOCH_3$), 6.96 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.28, (1H, dd, *J* 7.8, 4.8, C(5)*H*), 7.51 (2H, d, *J* 8.8, C(2)Ar(2,6)*H*), 8.05 (1H, dd, *J* 7.8, 1.8, C(4)*H*), 8.74 (1H, dd, *J* 4.8, 1.8, C(6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 52.5 (CO_2CH_3), 55.4 ($ArOCH_3$), 113.8 (C(2)Ar*C*(3,5)H), 121.1 (*C*(5)H), 126.7 (*C*(3)), 130.1 (C(2)Ar*C*(2,6)H), 132.5 (C(2)Ar*C*(1)), 138.0 (*C*(4)H), 151.4 (*C*(6)H), 158.3 (*C*(2)), 160.3 (C(2)Ar*C*(4)), 169.1 (CO_2Me); HRMS (NSI^+) $C_{14}H_{14}NO_3$ ($[M+H]^+$) requires 244.0968 found 244.0967 (−0.5 ppm).

Methyl 2-(4-methoxyphenyl)-5-phenylnicotinate



359

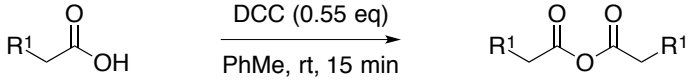
Following the procedure from Yoshida *et al*.[80] To a solution of **341** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), DPPP (4 mg, 0.01 mmol), and Et_3N (140 µL, 1.0 mmol), in DMF (1.3 mL) was added formic acid (23 µL, 0.6 mmol). The reaction was heated in a screw top vial for 16 h at 100 °C. Once cooled, the reaction mixture was quenched with brine and extracted with EtOAc (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated

under reduced pressure. Chromatographic purification (EtOAc:Petrol 5:95) gave the title compound as white solid (47 mg, 73%); mp 142-145 °C; ν_{max} (ATR)/cm^{-1} 1246, 1435 (C-O), 1709 (C=O), 2835, 2945, 3001 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.77 (3H, s, CO_2CH_3), 3.87 (3H, s, $ArOCH_3$), 6.99 (2H, d, *J* 8.6, C(2)Ar(3,5)*H*), 7.42-7.45 (1H, m, C(5)Ar(4)*H*), 7.51 (2H, t, *J* 7.6, C(2)Ar(2,6)*H*), 7.57 (2H, d, *J* 8.6, C(5)Ar(3,5)*H*), 7.65 (2H, d, *J* 7.4, C(5)Ar(2,6)*H*), 8.25 (1H, d, *J* 2.2, C(4)*H*), 8.97 (1H, d, *J* 2.2, C(6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 52.6 (CO_2CH_3), 55.5 ($ArOCH_3$), 113.9 (C(2)Ar*C*(3,5)H), 126.6 (*C*(3)), 127.2 (C(5)Ar*C*(2,6)H), 128.6 (C(5)Ar*C*(4)H), 129.4 (C(5)Ar*C*(3,5)H), 130.1 (C(2)Ar*C*(2,6)H), 132.1 (C(2)Ar*C*(1)), 134.2 (*C*(5)), 136.2 (*C*(4)H), 136.7 (*C*(5)Ar*C*(1)), 149.6 (*C*(6)H), 156.8 (*C*(2)), 160.4 (C(2)Ar*C*(4)), 169.1 (CO_2Me); HRMS (NSI$^+$) $C_{20}H_{18}NO_3$ ([M+H]$^+$) requires 320.1286 found 320.1290 (−0.6 ppm).

9.4 Experimental for Chapter 4

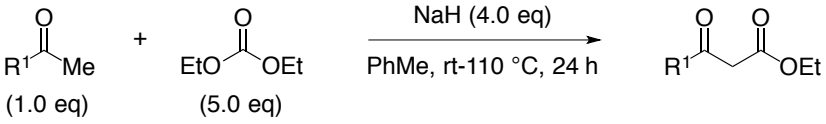
9.4.1 General Experimental Procedures

General Procedure J: *Preparation of Homoanhydrides*



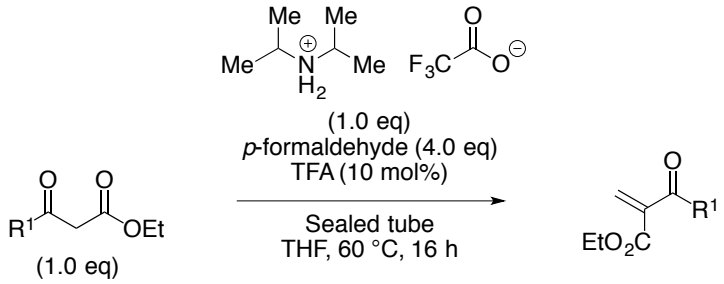
To a solution of requisite carboxylic acid (1.0 eq) in toluene (0.37 M) at rt was added DCC (0.55 eq) and the reaction stirred for 15 min. The reaction was filtered through Celite (eluent toluene) and concentrated under reduced pressure to give crude reaction mixture. Products were purified by recrystallisation if required.

General Procedure K: *Preparation of keto esters*



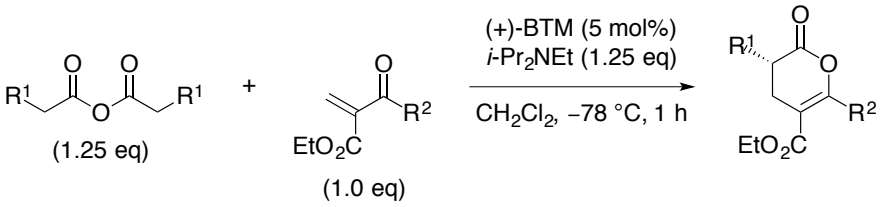
Following the literature procedure of Bretner and co-workers,[95] to a solution of ketone in toluene (0.42 M in ketone) at 0 °C was added NaH (60% w/w in mineral oil, 4.0 eq) and reaction warmed to rt and stirred for 2 h. Reaction mixture was added dropwise to a solution of diethyl carbonate (5.0 eq) in toluene [6.3 M in carbonate] and reaction stirred at reflux for 24 h. Once cooled the reaction mixture was quenched slowly with H_2O, acidified with HCl (2 M in H_2O) and extracted with EtOAc (×3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Products were purified by column chromatography in the solvent system reported.

General Procedure L: *Preparation of ethyl aroylacrylates*



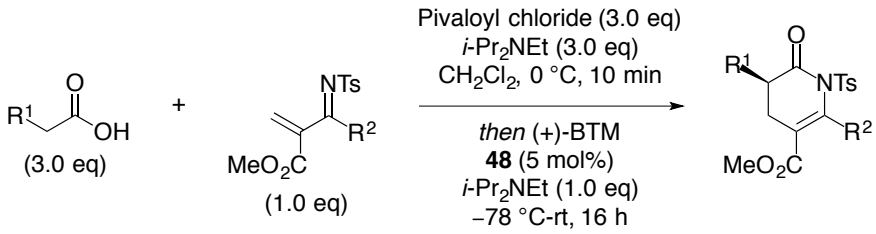
Keto ester (1.0 eq), diisopropylammonium 2,2,2-trifluoroacetate (1.0 eq), paraformaldehyde (4 eq) and TFA (0.1 eq) were added to THF (0.67 M in keto ester) in a sealable reaction tube. The reaction mixture was sealed and heated at reflux for 24 h. Once cooled the reaction mixture was diluted with H_2O and extracted with EtOAc (×3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Products were purified by column chromatography in the solvent system reported.

General Procedure M: *Isothiourea-catalysed Michael addition-lactonisation*



To a solution of requisite homoanhydride (1.25 eq) in CH_2Cl_2 (0.31 M) at −78 °C was added Lewis base catalyst (5 mol%) and reaction stirred for 20 min. A solution of Michael acceptor (1.0 eq) in CH_2Cl_2 (0.25 M), pre-cooled to −78 °C, is added followed by a solution of *i*-Pr_2NEt (1.25 eq) in CH_2Cl_2 (0.31 M), also pre-cooled to −78 °C, and reaction stirred until complete by TLC analysis. The reaction was quenched with aq. HCl (1 M), extracted with CH_2Cl_2 (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude residue. Products were purified by Biotage® Isolera™ 4 in the solvent system reported.

General Procedure N: *Isothiourea-catalysed Michael addition-lactamisation*

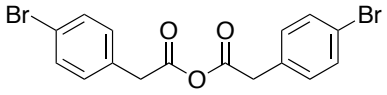


To a solution of requisite carboxylic acid (2.0 eq) in CH_2Cl_2 (0.1 M in carboxylic acid) at 0 °C was added *i*-Pr_2NEt (3.0 eq) and pivaloyl chloride (3.0 eq). The reaction was left to stir for 10 min before being cooled to −78 °C at which point Lewis base catalyst (5 mol%) and Michael

acceptor (1.0 eq) and *i*-Pr_2NEt (1.0 eq) were added and reaction was warmed to room temperature over 16 h. The reaction was quenched with HCl (1 M in H_2O), extracted with CH_2Cl_2 (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude residue. Products were purified by column chromatography in the solvent system reported.

9.4.2 Preparation of Homoanhydrides

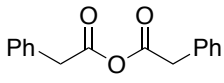
2-(4-Bromophenyl)acetic anhydride



383

Following general procedure J, 4-bromophenylacetic acid (1.00 g, 4.65 mmol) and DCC (528 mg, 2.56 mmol) in toluene (20 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (0.97 g, 97%); mp 75-77 °C; {lit.[2] mp 76-78 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) 3.61 (4H, s, CH_2), 6.98–7.03 (4H, m, Ar(3,5)*H*), 7.36–7.41 (4H, m, Ar(2,6)*H*). All data are in accordance with the literature.[2]

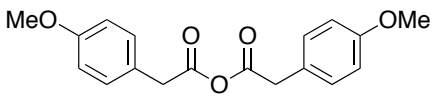
2-Phenylacetic anhydride



675

Following general procedure J, phenylacetic acid (1.00 g, 7.34 mmol) and DCC (757 mg, 3.67 mmol) in toluene (20 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (1.70 g, 91%); mp 70-72 °C; {lit.[179] mp 72-72.5 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 3.76 (4H, s, CH_2), 7.23–7.25 (4H, m, Ar(3,5)*H*), 7.32–7.38 (6H, m, Ar(4)*H* and Ar(2,6)*H*). All data are in accordance with the literature.[179]

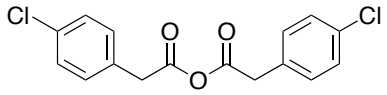
2-(4-Methoxyphenyl)acetic anhydride



676

Following general procedure J, 4-methoxyphenylacetic acid (1.00 g, 6.00 mmol) and DCC (681 mg, 3.30 mmol) in toluene (25 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (1.70 g, 90%); mp 61-62 °C; {lit.[179] mp 60-62 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 3.66 (4H, s, CH_2), 3.80 (4H, s, CH_2), 6.83–6.86 (4H, m, Ar(3,5)*H*), 7.10–7.13 (4H, m, Ar(2,6)*H*). All data are in accordance with the literature.[179]

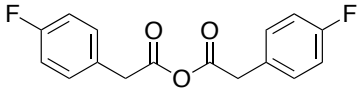
2-(4-Chlorophenyl)acetic anhydride



677

Following general procedure J, 4-chlorophenylacetic acid (1.00 g, 5.90 mmol) and DCC (669 mg, 3.25 mmol) in toluene (50 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (0.94 g, 98%); mp 62-64 °C; {lit.[179] mp 62-64 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 3.70 (4H, s, CH_2), 7.13 (4H, d, *J* 8.5, Ar(3,5)*H*), 7.28-7.31 (4H, m, Ar(2,6)*H*). All data are in accordance with the literature.[179]

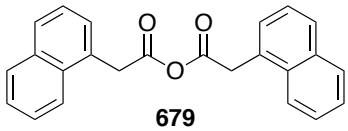
2-(4-Fluorophenyl)acetic anhydride



678

Following general procedure J, 4-chlorophenylacetic acid (1.00 g, 6.49 mmol) and DCC (737 mg, 3.57 mmol) in toluene (20 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (1.46 g, 77%); mp 34-36 ^{o}C; {lit.[179] mp 36-38 ^{o}C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.70 (4H, s, CH_2), 6.99-7.05 (4H, m, Ar(3,5)*H*), 7.16-7.19 (4H, m, Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[179]

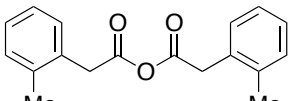
2-(Naphthalen-1-yl)acetic anhydride



679

Following general procedure J, 1-naphthylacetic acid (2.00 g, 10.8 mmol) and DCC (1.23 g, 5.94 mmol) in toluene (50 mL) gave crude reaction mixture. Recrystallisation (Et_2O) gave title compound as white solid (2.26 g, 59%); mp 34-36 °C; {lit.[180] mp 36-38 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.30 (4H, C(2)*H*), 7.23 (2H, d, *J* 6.9, Ar(1)*H*), 7.33-7.36 (2H, m, Ar(8)*H*), 7.47-7.50 (6H, m, Ar*H*), 7.79-7.82 (4H, m, Ar*H*), 7.86-7.87 (2H, m, Ar*H*). All data are in accordance with the literature.[180]

2-(2-Tolyl)acetic anhydride

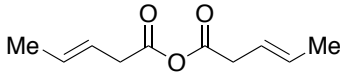


680

Following general procedure J, 2-tolylphenylacetic acid (2.00 g, 16.6 mmol) and DCC (1.88 mg, 9.13 mmol) in toluene (70 mL) gave crude reaction mixture as yellow oil that was used

immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) 2.74 (6H, s, ArCH_3), 3.72 (4H, s, C(2)*H*), 7.09-7.21 (8H, m, Ar*H*). Compound was **679** used immediately without further purification or analysis due to instability.

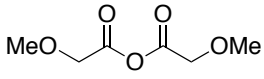
(*E*)-Pent-3-enoic anhydride



681

Following general procedure J, 3-pentenoic acid (1.13 g, 11.1 mmol) and DCC (1.17 g, 5.67 mmol) in toluene (33 mL) gave title compound as pale yellow oil (2.00 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.69-1.73 (6H, m, CH_3), 3.11-3.20 (4H, m, C(2)H_2), 5.42-5.57 (2H, m, C(4)*H*), 5.57-5.70 (2H, m, C(3)*H*). Spectroscopic data are in accordance with the literature.[181]

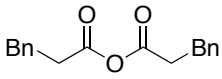
2-Methoxyacetic anhydride



682

Following general procedure J, 4-chlorophenylacetic acid (1.00 g, 11.1 mmol) and DCC (1.26 g, 6.11 mmol) in toluene (46 mL) gave crude reaction mixture as colourless oil that was used immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) 3.48 (6H, s, OCH_3), 4.18 (4H, s, C(2)H_2). Due to instability this compound was used immediately without further characterisation.

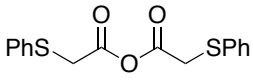
3-Phenylpropanoic anhydride



683

Following general procedure J, 3-phenylpropanoic acid (1.00 g, 6.66 mmol) and DCC (756 mg, 3.66 mmol) in toluene (28 mL) gave title compound as pale yellow oil (2.00 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) 2.74 (4H, t, *J* 8.0, C(2)H_2), 2.96 (4H, t, *J* 8.0, C(3)H_2), 7.17-7.33 (10H, m, Ar*H*). All data are in accordance with the literature.[182]

2-(Phenylthio)acetic anhydride

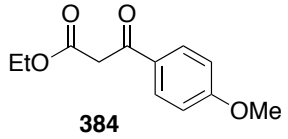


684

Following general procedure J, (phenylthio)acetic acid (2.00 g, 11.9 mmol) and DCC (1.35 g, 6.54 mmol) in toluene (50 mL) gave title compound as pale yellow oil (3.79 g, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) 3.75 (4H, s, C(2)H_2), 7.23-7.35 (6H, m, Ar*H*), 7.38-7.40 (4H, m, Ar*H*). Due to instability this compound was used immediately without further characterisation.

9.4.3 Preparation of Keto Esters

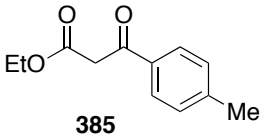
Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate



384

Following general procedure K, 4-methoxyacetophenone (5.00 g, 33.3 mmol) in toluene (79 mL), NaH (3.19 g, 133 mmol), diethyl carbonate (20 mL, 166 mmol) in toluene (25 mL) gave crude product. Column chromatography (10:90 EtOAc:hexane) gave the title compound as a yellow oil as a (5.55 g, 75%, 2.5:1 keto:enol tautomeric mixture); ^{1}H NMR (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, keto $CO_2CH_2CH_3$), 1.33 (1.2H, t, *J* 7.1, enol $CO_2CH_2CH_3$), 3.85 (1.2H, s, enol $ArOCH_3$), 3.88 (3H, s, keto $ArOCH_3$), 3.94 (2H, s, keto C(2)*H*), 4.17-4.29 (2.8H, m, keto $CO_2CH_2CH_3$ and enol $CO_2CH_2CH_3$), 5.58 (0.4H, s, enol C(2)*H*), 6.91-6.96 (2.8H, m, keto Ar(3,5)*H* and enol Ar(3,5)*H*), 7.74 (0.8H, d, *J* 7.7, enol Ar(2,6)*H*), 7.93 (2H, d, *J* 9.0, keto Ar(2,6)*H*), 12.6 (0.4H, s, enol O*H*). All data in accordance with literature.[183]

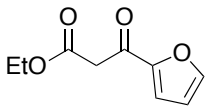
Ethyl 3-oxo-3-(*p*-tolyl)propanoate



385

Following general procedure K, 4-methylacetophenone (2.97 mL, 22.4 mmol) in toluene (53 mL), NaH (3.58 g, 89.6 mmol), diethyl carbonate (13.6 mL, 112 mmol) in toluene (18 mL) gave crude product. Column chromatography (7.5:92.5 EtOAc:hexane) gave the title compound as a yellow oil as a (6.02 g, 78%); ^{1}H NMR (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.42 ($ArCH_3$), 3.96 (2H, s, C(2)*H*), 4.21 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 7.28 (2H, d, *J* 8.0, Ar(3,5)*H*), 7.85 (2H, d, *J* 8.3, Ar(2,6)*H*). All data in accordance with literature.[183]

Ethyl 3-(furan-2-yl)-3-oxopropanoate

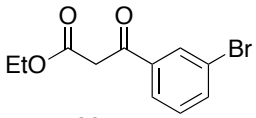


386

To a solution of 2-acetylfuran (3.00 g, 27.2 mmol) in diethyl carbonate (54.4 mL) was added NaH (2.72 g, 68.0 m mmol) and the reaction stirred at rt for 1 h. Reaction was then heated to 90

°C and stirred for further 2 h. The reaction was cooled and quenched with H_2O, acidified to pH 5 and extracted with EtOAc (×3). Combined organics were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give crude mixture. Column chromatography (EtOAc:hexane 10:90) gave the title compound as a brown oil as a (2.43 g, 49%, 2:1 keto:enol tautomeric mixture); ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.84 (2H, s, C(2)H_2), 4.20 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.57 (1H, dd, *J* 3.6, 1.6, Ar(4)*H*), 7.27 (1H, d, *J* 3.59, Ar(3)*H*), 7.61 (1H, s, Ar(5)*H*). All data in accordance with literature.[184]

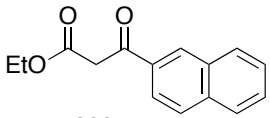
Ethyl 3-(3-bromophenyl)-3-oxopropanoate



387

Following general procedure K, 4-bromoacetophenone (3.00 g, 15.1 mmol) in toluene (36 mL), NaH (1.45 g, 60.4 mmol), diethyl carbonate (9.16 mL, 75.5 mmol) in toluene (12 mL) gave crude product. Column chromatography (7.5:92.5 EtOAc:hexane,) gave the title compound as a yellow oil as a (2.05 g, 50%, 2:1 keto:enol tautomeric mixture); ^{1}H NMR (500 MHz, $CDCl_3$) 1.24-1.36 (4.5H, t, *J* 7.1, keto $CO_2CH_2CH_3$ enol $CO_2CH_2CH_3$), 3.96 (2H, s, keto C(2)*H*), 4.18-4.28 (3H, m, keto $CO_2CH_2CH_3$ and enol $CO_2CH_2CH_3$), 5.65 (0.5H, s, enol C(2)*H*), 7.29-7.40 (1.5H, m, keto Ar(5)*H* and enol Ar(5)*H*), 7.58 (0.5H, ddd, *J* 8.0, 2.0, 1.0, enol Ar(4)*H*), 7.67-7.74 (1.5H, m, keto Ar(4)*H* and enol Ar(6)*H*), 7.86 (1H, dt, *J* 7.8, 1.3, keto Ar(6)*H*), 7.92 (0.5H, t, *J* 1.8, enol Ar(2)*H*), 8.08 (1H, t, *J* 1.8, keto C(2)*H*), 12.5 (0.5H, s, enol O*H*). All data in accordance with literature.[185]

Ethyl 3-(naphthalen-2-yl)-3-oxopropanoate

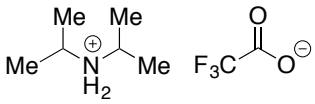


388

Following general procedure K, 4-acetylnaphthalene (3.00 g, 17.6 mmol) in toluene (42 mL), NaH (2.82 g, 70.4 mmol), diethyl carbonate (10.7 mL, 88.1 mmol) in toluene (14 mL) gave crude product. Column chromatography (EtOAc:hexane 10:90) gave the title compound as a yellow oil as a (2.56 g, 60%, 4:1 keto:enol tautomeric mixture); ^{1}H NMR (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, keto $CO_2CH_2CH_3$), 4.13 (2H, s, keto C(2)H_2), 4.24 (2H, q, *J* 7.1, keto $CO_2CH_2CH_3$), 7.56-7.59 (1H, td, *J* 7.6, 7.0, 1.2, keto Ar*H*), 7.61-7.64 (1H, m, keto Ar*H*), 7.88-7.92 (2H, m, keto Ar*H*), 7.98 (1H, d, *J* 8.1, keto Ar*H*), 8.02 (1H, dd, *J* 8.6, 1.8, keto Ar*H*), 8.46 (1H, s, keto Ar*H*). All data in accordance with literature.[184]

9.4.4 Preparation of Aroyl Acrylates

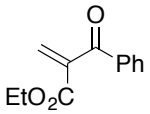
Diisopropylammonium 2,2,2-trifluoroacetate



689

Following literature procedure,[96] to a solution of DIPA (14.1 mL, 100 mmol) in Et_2O (100 mL) at 0 °C was added TFA (7.70 mL, 100 mmol) dropwise and the reaction mixture was stirred for 5 min at 0 °C. The reaction mixture was filtered and the resulting solid was washed with cold Et_2O and dried under reduced pressure to give the title compound (18.4 g, 86%) as a white solid; mp 120-122 °C {Lit.[96] mp 122-123 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 1.31 (12H, d, *J* 6.7, 4 CH_3), 3.35 (2H, septet, *J* 6.7, 2 C*H*), 8.92 (2H, s, NH_2). All data in accordance with literature.[96]

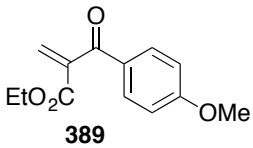
Ethyl 2-benzoylacrylate



378

Following general procedure L, ethyl benzoylacetate (1.73 mL, 10.0 mmol), diisopropylammonium 2,2,2-trifluoroacetate (2.15 g, 10.0 mmol), paraformaldehyde (1.20 g, 40 mmol) and TFA (77 μL, 1.00 mmol) in THF (60 mL) gave crude product. Column chromatography (10:90 Petrol:EtOAc) to give the title compound (1.80 g, 89%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, CH_3), 4.22 (2H, q, *J* 7.1, CH_2CH$_3$), 6.07 (1H, d, *J* 0.8, =C*H*H), 6.70 (1H, d, *J* 0.8, =CH*H*), 7.47 (2H, t, *J* 7.8, ArC(3,5)H), 7.56-7.65 (1H, m, ArC(4)*H*), 7.86 (2H, d, *J* 8.1, ArC(2,6)*H*). All data in accordance with literature.[186]

Ethyl 2-(4-methoxybenzoyl)acrylate

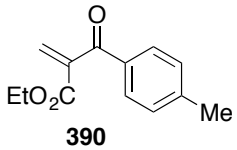


389

Following general procedure L, ethyl 3-(4-methoxyphenyl)-3-oxopropanoate **384** (2.00 mL, 9.43 mmol), diisopropylammonium 2,2,2-trifluoroacetate (2.03 g, 9.43 mmol), paraformaldehyde (1.13 g, 37.7 mmol) and TFA (74 μL, 0.94 mmol) in THF (60 mL) gave crude product. Column chromatography (10:90 Petrol:EtOAc) to give the title compound (1.80 g, 89%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, CH_3), 3.88 (3H, s, ArOCH_3), 4.23 (2H, q, *J* 7.1, CH_2CH$_3$), 6.00 (1H, d, *J* 0.7, =C*H*H), 6.66 (1H, d, *J* 0.7, =CH*H*),

6.94 (2H, d, *J* 9.0, ArC(3,5)H), 7.86 (2H, d, *J* 9.0, ArC(2,6)*H*). All data in accordance with literature.[186]

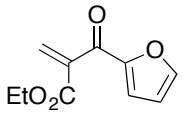
Ethyl 2-(4-methylbenzoyl)acrylate



390

Following general procedure L, ethyl 3-(4-tolyl)-3-oxopropanoate **385** (2.0 g, 9.69 mmol), diisopropylammonium 2,2,2-trifluoroacetate (2.08 g, 9.69 mmol), paraformaldehyde (1.17 g, 38.8 mmol) and TFA (75μL, 0.97 mmol) in THF (60 mL) gave crude product. Column chromatography (10:90 Petrol:EtOAc) to give the title compound (1.23 g, 61%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 4.13 (2H, q, *J* 7.2, 6.03 (1H, d, *J* 0.7, =C*H*H), 6.68 (1H, d, *J* 0.7, =CH*H*), 7.26 (2H, d, *J* 8.2, Ar(3,5)*H*), 7.77 (2H, d, *J* 8.2, Ar(2,6)*H*). All data in accordance with literature.[186]

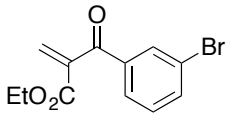
Ethyl 2-(furan-2-carbonyl)acrylate



391

Following general procedure L, ethyl 3-(furan-2-yl)-3-oxopropanoate **386** (1.50 g, 8.23 mmol), diisopropylammonium 2,2,2-trifluoroacetate (1.77 g, 8.23 mmol), paraformaldehyde (987 mg, 32.9 mmol) and TFA (92 μL, 0.82 mmol) in THF (60 mL) gave crude product. Column chromatography (15:85 Petrol:EtOAc) to give the title compound (766 g, 48%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 4.27 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.21 (1H, d, *J* 0.7, =C*H*H), 6.57 (1H, dd, *J* 3.6, 1.7, Ar(4)*H*), 6.66 (1H, d, *J* 0.7, =CH*H*), 7.20 (1H, dd, *J* 3.6, 0.8, Ar(3)*H*), 7.65 (1H, dd, *J* 1.7, 0.8, Ar(5)*H*). All data in accordance with literature.[186]

Ethyl 2-(3-bromobenzoyl)acrylate

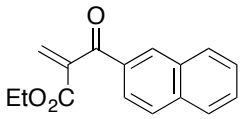


392

Following general procedure L, ethyl 3-(3-bromophenyl)-3-oxopropanoate **387** (2.05 g, 7.56 mmol), diisopropylammonium 2,2,2-trifluoroacetate (1.63 g, 7.56 mmol), paraformaldehyde (906 mg, 30.2 mmol) and TFA (57 μL, 0.76 mmol) in THF (60 mL) gave crude product. Column chromatography (10:90 Petrol:EtOAc) to give the title compound (447 mg, 21%) as a

yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.1, C*H*$_3$), 4.24 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 6.10 (1H, s, =C*H*H), 6.72 (1H, d, *J* 0.7, =CH*H*), 7.35 (1H, t, *J* 7.9, Ar(5)*H*), 7.72 (1H, ddd, *J* 8.0, 1.9, 1.0, Ar(5)*H*), 7.76 (1H, dt, *J* 7.8, 1.3, Ar(2)*H*), 7.99 (1H, t, *J* 1.8, Ar(2)*H*). All data in accordance with literature.[186]

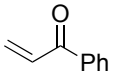
Ethyl 2-(2-naphthoyl)acrylate



393

Following general procedure L, ethyl 3-(naphthalen-2-yl)-3-oxopropanoate **388** (2.00 g, 8.30 mmol), diisopropylammonium 2,2,2-trifluoroacetate (1.78 g, 8.30 mmol), paraformaldehyde (997 mg, 33.2 mmol) and TFA (64 μL, 0.83 mmol) in THF (60 mL) gave crude product. Column chromatography (10:90 Petrol:EtOAc) to give the title compound (1.01 g, 50%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, C*H*$_3$), 4.24 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 6.13 (1H, d, *J* 0.6, =C*H*H), 6.78 (1H, d, *J* 0.6, =CH*H*), 7.56 (1H, ddd, *J* 8.1, 6.9, 1.2, Ar*H*), 7.63 (1H, ddd, *J* 8.2, 6.2, 1.3, Ar*H*), 7.89-8.00 (4H, m, Ar*H*), 8.33 (1H, s, Ar*H*). All data in accordance with literature.[186]

1-phenylprop-2-en-1-one

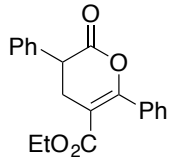


417

To a solution of 3-chloro-1-phenylpropan-1-one (1.00 g, 5.93 mmol) in $CHCl_3$ (13 mL) was added Et_3N (2.07 mL, 14.8 mmol) and reaction stirred at rt for 16 h. Reaction quenched with aq. HCl (1 M), extracted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ and brine then dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a yellow oil (781 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) 5.94 (1H, dd, *J* 1.7, 10.5, C(3)*H*^{a}H^b), 6.45 (1H, dd, *J* 1.8, 17.1, C(3)H^a*H*^{b}), 7.17 (1H, dd, *J* 10.4, 17.1, C(2)*H*), 7.46-7.52 (2H, m, Ar(3,6)*H*), 7.55-7.61 (1H, m, Ar(4)*H*), 7.94-7.97 (2H, m, Ar(2,6)*H*). All data in accordance with literature.[98]

9.4.5 Enantioselective Isothiourea-Catalysed Michael Addition Lactonisation

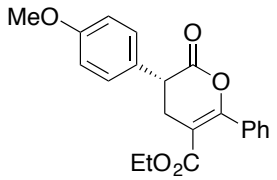
Ethyl (*R*)-2-oxo-3,6-diphenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



379

Following general procedure M, homoanhydride **675** (155 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-benzoylacrylate **378** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (106 μL, 0.61 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (44 mg, 69%) as a white solid. mp 120-122 °C; ν_{max} (ATR)/cm^{-1} 3057, 2980 (C-H), 1769 (C=O dihydropyranone), 1692 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.05-3.23 (2H, m, C(4)*H*H and C(4)H*H*), 3.99 (1H, dd, *J* 10.9, 7.0, C(3)*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 7.29-7.48 (10H, m, ArC*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 13.8 (CH_3), 29.2 (*C*(4)), 44.4 (*C*(3)), 61.1 (CH_2CH_3), 108.8 (*C*(5)), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.1 (Ar*C*), 128.8 (Ar*C*), 129.1 (Ar*C*), 130.1 (Ar*C*), 133.1 (C(6)Ar*C*(1)), 135.8 (C(3)Ar*C*(1)), 158.6 (Ar*C*(6)), 166.4 (CO_2Et), 168.2 (*C*(2)); HRMS (NSI^+) $C_{20}H_{19}O_4$ $[M+H]^+$, found 323.1275, requires 323.1278 (−0.9 ppm).

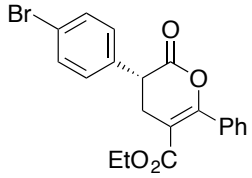
Ethyl (*R*)-3-(4-methoxyphenyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



397

Following general procedure M, homoanhydride **676** (198 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-benzoylacrylate **378** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (106 μL, 0.61 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (143 mg, 83%) as a white solid. mp 113-115 °C; $[\alpha]_D^{20}$ −32.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_S (3*S*): 33.7 min, t_R (3*R*): 37.5 min; 91% ee; ν_{max} (ATR) 3001, 2837 (C-H), 1775 (C=O dihydropyranone), 1717 (C=O Ester); ^{1}H NMR (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.11-3.18 (2H, m, C(4)*H*H and C(4)H*H*), 3.82 (3H, s, $ArOCH_3$), 3.94 (1H, dd, *J* 10.7, 7.0, C(3)*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.93 (2H, d, *J* 8.8, C(3)Ar(3,5)*H*), 7.25 (2H, d, *J* 8.7, C(3)Ar(2,6)*H*), 7.36-7.45 (5H, m, C(6)Ar(3,5)*H* and C(6)Ar(2,6)*H* and C(6)Ar(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.3 (*C*(4)HH), 43.6 (*C*(3)H), 55.5 ($ArOCH_3$), 61.1 ($CO_2CH_2CH_3$), 108.8 (*C*(5)), 114.5 (C(3)Ar*C*(3,5)H), 127.8 (C(6)Ar*C*(4)H), 128.0 (C(6)Ar*C*(2,6)H), 128.8 (C(6)Ar*C*(3,5)H), 129.2 (C(3)Ar*C*(2,6)H), 130.1 (C(6)Ar*C*(1)), 133.1 (C(3)Ar*C*(1)), 158.6 (*C*(6)), 159.4 (C(3)Ar*C*(4)OMe), 166.5 (CO_2Et), 168.5 (*C*(2)); HRMS (NSI^+) $C_{21}H_{20}O_5Na$ $[M+Na]^+$, found 375.1208, requires 375.1203 (+1.3 ppm).

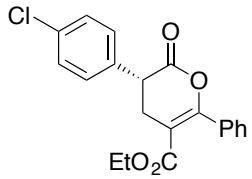
Ethyl (*R*)-3-(4-bromophenyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



380

Following general procedure M, homoanhydride **383** (80 mg, 0.30 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (3 mg, 0.012 mmol) ethyl 2-benzoylacrylate **378** (50 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (52 μL, 0.30 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (44 mg, 69%) as a white solid. mp 176-177 °C; $[\alpha]_D^{20}$ −42.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*R*): 13.6 min, t_R(*S*): 15.5 min, 90% ee; ν_{max} (ATR) 2984, 2905 (C-H), 1769 (C=O dihydropyranone), 1694 (C=O Ester); ^{1}H NMR (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.06 (1H, dd, *J* 17.2, 11.4, C(4)*H*H), 3.16 (1H, dd, *J* 17.2, 6.8, C(4)H*H*), 3.94 (1H, dd, *J* 11.3, 6.8, C(3)*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 7.20 (2H, d, *J* C(3)Ar(2,6)*H*), 7.37-7.45 (5H, m, C(6)Ar(3,5)*H* and C(6)Ar(2,6)*H* and C(6)Ar(4)*H*), 7.53 (2H, d, *J* 8.4, C(3)Ar(3,5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.1 (*C*(4)HH), 43.9 (ArO*C*H_3), 61.2 ($CO_2CH_2CH_3$), 108.7 (*C*(5)), 122.3 (C(3)Ar*C*(4)), 128.1 (C(6)Ar*C*(2,6)H), 128.8 (C(6)Ar*C*(3,5)H), 129.9 (C(3)Ar*C* (3,5)H), 130.3 (C(6)Ar*C*(4)H), 132.2 (C(3)Ar*C*(2,6)H), 132.9 (C(6)Ar*C*(1)), 134.8 (C(3)Ar*C*(1)), 158.7 (*C*(6)), 166.3 (CO_2Et), 167.7 (*C*(2)); HRMS (NSI^+) $C_{20}H_{17}BrO_4Na$ $[M+Na]^+$, found 423.0198, requires 423.0202 (−1.0 ppm).

Ethyl (*R*)-3-(4-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate

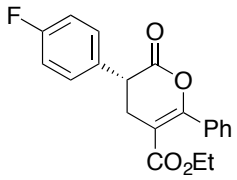


395

Following general procedure M, homoanhydride **677** (197 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-benzoylacrylate **378** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (106 μL) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (148 mg, 85%) as a white solid. mp 168-170 °C; $[\alpha]_D^{20}$ −21.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1

mLmin^{-1}, 220 nm, 30 °C) t_R(*R*): 29.9 min, t_R(*S*): 34.3 min, 88% ee; ν_{max} (ATR) 2980 (C-H), 1752 (C=O dihydropyranone), 1697 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.07 (1H, dd, *J* 17.2, 11.4, C(4)*H*H), 3.16 (1H, dd, *J* 17.2, 6.8, C(4)H*H*), 3.96 (1H, dd, *J* 11.3, 6.8, C(3)*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 7.27 (2H, d, *J* 6.9, C(3)Ar(3,5)*H*), 7.37-7.45 (7H, m, C(6)Ar(3,5)*H* and C(3)Ar(2,6)*H* and C(6)Ar(4)*H* and C(6)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.2 (*C*(4)HH), 43.8 (*C*(3)H), 61.2 ($CO_2CH_2CH_3$), 108.7 (*C*(5)), 128.1 (C(6)Ar*C*(2,6)H), 128.8 (C(6)Ar*C*(3,5)H), 129.3 (C(3)Ar*C*(3,5)H), 129.6 (C(6)Ar*C*(4)H), 130.3 (C(3)Ar*C*(2,6)), 132.9 (C(3)Ar*C*(4)), 134.2 (C(3)Ar*C*(1)), 134.2 (C(6)Ar*C*(1)), 158.7 (*C*(6)), 166.3 (CO_2Et), 167.9 (*C*(2)); HRMS (APCI$^+$) $C_{20}H_{18}Cl^{35}O_4$ $[M+H]^+$, found 357.0888, requires 357.0888 (0.0 ppm).

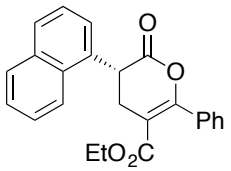
Ethyl (*R*)-3-(4-fluorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



396

Following general procedure M, homoanhydride **678** (177 mg, 0.61 mmol), (+)-BTM (5 mg, 0.025 mmol) and *i*-Pr_2NEt (206 μL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] the title compound (128 mg, 77%) as a white solid. mp 120-122 °C; $[\alpha]_D^{20}$ −11.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R*): 9.1 min, t_R(*S*): 12.5 min, 49% ee; ν_{max} (ATR)/cm^{-1} 2986 (C-H), 1771 (C=O dihydropyranone), 1694 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.07 (1H, dd, *J* 17.2, 11.4, C(4)*H*H), 3.16 (1H, dd, *J* 17.2, 6.8, C(4)H*H*), 3.97 (1H, dd, *J* 11.4, 6.8, C(3)*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 7.10 (2H, t, *J* 8.6, C(3)Ar(3,5)*H*), 7.30 (2H, dd, *J* 8.5, 5.3, C(3)Ar(2,6)*H*), 7.37-7.45 (5H, m, C(6)Ar(3,5)*H* and C(6)Ar(2,6)*H* and C(6)Ar(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.3 (*C*(4)HH), 43.7 (Ar*O*CH_3), 61.2 ($CO_2CH_2CH_3$), 108.8 (*C*(5)), 116.1 (d, *J* 21.7, C(3)Ar*C*(3,5)H), 128.1 (C(6)Ar*C*(2,6)H), 128.8 (C(6)Ar*C*(3,5)H), 129.9 (d, *J* 8.2, C(3)Ar*C*(2,6)H), 130.2 (C(6)Ar*C*(4)H), 131.6 (C(3)Ar*C*(1)), 133.0 (C(6)Ar*C*(1)), 158.6 (*C*(6)), 162.5 (d, *J* 247, C(3)Ar*C*(4)F), 166.4 (CO_2Et), 168.1 (*C*(2)); ^{19}F NMR (282 MHz, $CDCl_3$) −114.0 (Ar*F*); HRMS (NSI$^+$) $C_{20}H_{17}FO_4Na$ $[M+Na]^+$, found 363.1002, requires 363.1003 (−0.3 ppm).

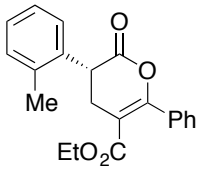
Ethyl (*R*)-3-(naphthalen-1-yl)-2-oxo-6-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



398

Following general procedure M, homoanhydride **679** (216 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-benzoylacrylate **278** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (106 μL, 0.61 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 80:20 10 CV, 80:20 3 CV)] gave the title compound (147 mg, 81%) as a white solid. mp 124-126 °C; $[\alpha]_D^{20}$ +6.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(*S*): 18.2 min, t_R(*R*): 26.3 min, 97% ee; ν_{max} (ATR) 3052, 2990 (C-H), 1759 (C=O dihydropyranone), 1705 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.25-3.34 (2H, m, C(4)*H*H and C(4)H*H*), 4.03 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.73 (1H, dd, *J* 10.3, 8.1, C(3)*H*), 7.41-7.59 (9H, m, Ar*H*), 7.86-7.88 (1H, m, Ar*H*), 7.92 (1H, d, *J* 8.0, Ar*H*), 7.96 (1H, d, *J* 8.4, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.2 (*C*(4)HH), 41.1 (*C*(3)*H*), 61.2 ($CO_2CH_2CH_3$), 109.0 (*C*(5)), 123.0 (Ar*C*H), 125.5 (Ar*C*H), 125.7 (Ar*C*H), 126.1 (Ar*C*H), 126.8 (Ar*C*H), 128.1 (Ar*C*H), 128.9 (Ar*C*H), 129.1 (Ar*C*H), 129.4 (Ar*C*H), 130.2 (Ar*C*H), 131.2 (Ar*C*), 132.1 (Ar*C*), 133.1 (Ar*C*), 134.2 (Ar*C*), 158.6 (*C*(6)), 166.4 (CO_2Et), 168.0 (*C*(2)); HRMS ($APCI^+$) $C_{24}H_{21}O_4$ $[M+H]^+$, found 373.1437, requires 373.1434 (+0.7 ppm).

Ethyl (*R*)-2-oxo-6-phenyl-3-(*o*-tolyl)-3,4-dihydro-2*H*-pyran-5-carboxylate

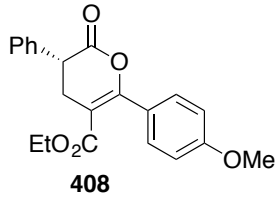


399

Following general procedure M, homoanhydride **680** (178 mg, 0.61 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-benzoylacrylate **278** (100 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (106 μL, 0.61 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 80:20 10 CV, 80:20 3 CV)] gave the title compound (134 mg, 81%) as a white solid. mp 100-102 °C; $[\alpha]_D^{20}$ −10.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OJ-H (70:30 hexane:IPA, flow rate 1 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*S*): 15.1 min, t_R(*R*): 24.4 min, 50% ee; ν_{max} (ATR) 2978

(C-H), 1767 (C=O dihydropyranone), 1694 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.06 (1H, dd, *J* 16.9, 12.6, C(4)*H*H), 3.13 (1H, dd, *J* 17.2, 7.3, C(4)H*H*), 4.04 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.14 (1H, dd, *J* 12.5, 7.3, C(3)*H*), 7.25-7.26 (4H, m, C(3)Ar(3)*H* and C(3)Ar(4)*H* and C(3)Ar(5)*H* and C(3)Ar(6)*H*), 7.39-7.50 (5H, m, C(6)Ar(3,5)*H* and C(6)Ar(2,6)*H* and C(6)Ar(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 19.9 ($ArCH_3$), 28.9 (*C*(4)HH), 41.3 (*C*(3)*H*), 61.2 ($CO_2CH_2CH_3$), 109.1 (*C*(5)), 126.8 (C(3)Ar*C*(5)H), 127.5 (C(3)Ar*C*(6)H), 128.1 (C(6)Ar*C*(3,5)H), 128.1 (C(3)Ar*C*(4)H), 128.9 (C(6)Ar*C*(2,6)H), 130.2 (C(6)Ar*C*(4)H), 131.1 (C(3)Ar*C*(3)H), 133.1 (C(3)Ar*C*(1)), 134.6 (C(6)Ar*C*(1)), 136.5 (C(3)Ar*C*(2)), 158.7 (*C*(6)), 166.4 (CO_2Et), 168.0 (*C*(2)); HRMS (APCI$^+$) $C_{21}H_{21}O_4$ $[M+H]^+$, found 337.1435, requires 337.1434 (+0.2 ppm).

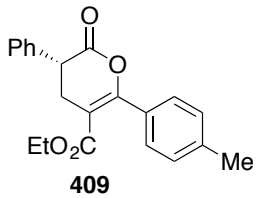
Ethyl (*R*)-6-(4-methoxyphenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate



408

Following general procedure M, homoanhydride **675** (140 mg, 0.53 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol) ethyl 2-(4-methoxybenzoyl)acrylate **389** (100 mg, 0.43 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (93 μL, 0.53 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera^{TM} 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (116 mg, 77%) as a white solid. mp 96-98 °C; $[\alpha]_D^{20}$ −63.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*S*): 12.1 min, t_R(*R*): 16.0 min, 91% ee; ν_{max} (ATR) 2978, 2968 (C-H), 1773 (C=O dihydropyranone), 1713 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.06-3.19 (2H, m, C(4)*H*H and C(4)H*H*), 3.84 (3H, s, $ArOCH_3$), 3.96 (1H, dd, *J* 11.1, 6.9, C(3)*H*), 4.08 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.90 (2H, d, *J* 8.8, C(6)Ar(3,5)*H*), 7.31-7.35 (3H, m, C(3)Ar(3,5)*H* and C(3)Ar(4)*H*), 7.39-7.42 (4H, m, C(3)Ar(2,6)*H* and C(6)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 29.5 (*C*(4)HH), 44.5 ($ArOCH_3$), 55.5 (*C*(3)H), 61.1 ($CO_2CH_2CH_3$), 107.8 (*C*(5)), 113.4 (C(6)Ar*C*(3,5)H), 125.2 (C(6)Ar*C*(1)), 128.1 (C(3)Ar*C*(4)H), 128.2 (C(3)Ar*C*(3,5)H), 129.1 (C(6)Ar*C*(2,6)H), 130.6 (C(3)Ar*C*(2,6)H), 136.0 (C(3)Ar*C*(1)), 158.5 (*C*(6)), 161.2 (C(6)Ar*C*(4)), 166.6 (CO_2Et), 168.5 (*C*(2)); HRMS (NSI$^+$) $C_{21}H_{20}O_5Na$ $[M+Na]^+$, found 375.1208, requires 375.1203 (+1.3 ppm).

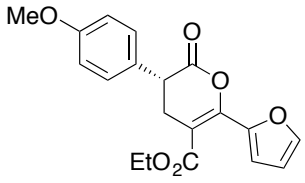
Ethyl (*R*)-2-oxo-3-phenyl-6-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-5-carboxylate



409

Following general procedure M, homoanhydride **675** (153 mg, 0.58 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.023 mmol) ethyl 2-(4-methylbenzoyl)acrylate **390** (100 mg, 0.46 mmol) in CH_2Cl_2 (2 mL) and Na_2CO_3 (61 mg, 0.58 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera^{TM} 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (101 mg, 69%) as a white solid. mp 72-74 °C; $[\alpha]_D^{20}$ −36.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*S*): 15.3 min, t_R(*R*): 18.8 min, 84% ee; ν_{max} (ATR) 2998, 2986 (C-H), 1755 (C=O dihydropyranone), 1717 (C=O Ester); ^{1}H NMR (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.39 (3H, s, $ArCH_3$), 3.06-3.19 (2H, m, C(4)*H*H and C(4)H*H*), 3.97 (1H, dd, *J* 10.8, 7.1, C(3)*H*), 4.06 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 7.18-7.20 (2H, m, C(6)Ar(3,5)*H*), 7.30-7.36 (5H, m, C(3)Ar(3,5)*H* and C(3)Ar(4)*H* and C(6)Ar(2,6)*H*), 7.38-7.42 (2H, m, C(6)Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 13.9 ($CO_2CH_2CH_3$), 21.6 ($ArCH_3$) 29.4 (*C*(4)HH), 44.4 ($ArOCH_3$), 61.1 ($CO_2CH_2CH_3$), 108.3 (*C*(5)), 128.1 (C(3)Ar*C*(4)H), 128.2 (C(6)Ar*C*(3,5)H), 128.7 (C(3)Ar*C*(3,5)H), 128.8 (C(6)Ar*C*(2,6)H), 129.1 (C(3)Ar*C*(2,6)H), 135.9 (C(6)Ar*C*(1)), 140.4 (C(3)Ar*C*(1)), 158.8 (*C*(6)), 166.5 (CO_2Et), 168.3 (*C*(2)); HRMS (NSI$^+$) $C_{21}H_{21}O_4$ $[M+H]^+$, found 337.1437, requires 337.1434 (+0.8 ppm).

Ethyl (*R*)-6-(furan-2-yl)-3-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate

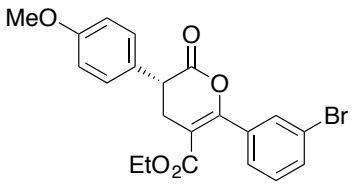


411

Following general procedure M, homoanhydride **676** (208 mg, 0.64 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol) ethyl 2-(furan-2-carbonyl)acrylate **391** (100 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (111 µL, 0.64 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera^{TM} 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (107 mg, 61%) as a white solid. mp 92-94 °C; $[\alpha]_D^{20}$ −34.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*R*): 17.6 min, t_S(*S*): 21.4 min, 99% ee; ν_{max} (ATR) 2980, 2941 (C-H), 1778 (C=O dihydropyranone), 1713 (C=O Ester); ^{1}H NMR (400

MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.01-3.13 (2H, m, C(4)*H*H and C(4)H*H*), 3.81 (3H, s, $ArOCH_3$), 3.90 (1H, dd, *J* 10.5, 7.6, C(3)*H*), 4.24 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.49 (1H, dd, *J* 3.5, 1.8, C(6)Ar(4)*H*), 6.89-6.93 (3H, m, C(6)Ar(3)*H* and C(3)Ar(3,5)*H*), 7.22 (2H, d, *J* 8.6, C(3)Ar(2,6)*H*), 7.48 (1H, dd, C(6)Ar(5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 29.8 (*C*(4)HH), 43.7 (*C*(3)H), 55.5 ($ArOCH_3$), 61.5 ($CO_2CH_2CH_3$), 108.0 (*C*(5)), 111.7 (C(6)Ar*C*(4)H), 113.6 (C(6)Ar*C*(3)H), 114.5 (C(3)Ar*C*(3,5)H), 127.7 (C(3)Ar*C*(1)), 129.3 (C(3)Ar*C*(2,6)H), 144.2 (C(6)Ar*C*(5)H) 145.5 (C(3)Ar*C*(4)), 146.2 (*C*(6)), 149.6 (C(6)Ar*C*(2)) 159.4 (C(3)Ar*C*(4)), 166.4 (CO_2Et), 168.1 (*C*(2)); HRMS (NSI^+) $C_{19}H_{18}O_6Na$ $[M+Na]^+$, found 365.1003, requires 365.0996 (+2.0 ppm).

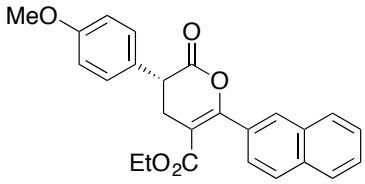
Ethyl (*R*)-6-(3-bromophenyl)-3-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate



413

Following general procedure M, homoanhydride **676** (243 mg, 0.44 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-(3-bromobenzoyl)acrylate **392** (100 mg 0.35 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (77 μL, 0.44 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (92 mg, 61%) as a white solid. mp 96-98 °C; $[\alpha]_D^{20}$ −33.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(*R*): 18.4 min, t_R(*S*): 26.2 min, 68% ee; ν_{max} (ATR) 2982, 2902 (C-H), 1773 (C=O dihydropyranone), 1697 (C=O Ester); ^1H NMR (400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.04-3.18 (2H, m, C(4)*H*H and C(4)H*H*), 3.82 (3H, s, $ArOCH_3$), 3.93 (1H, dd, *J* 10.8, 7.0, C(3)*H*), 4.06 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.94 (2H, d, *J* 8.8, C(3)Ar(3,5)*H*), 7.21-7.28 (3H, m, C(6)Ar(5)*H*) and C(3)Ar(2,6)*H*), 7.36 (1H, dt, 7.8, 1.3, C(6)Ar(4)*H*), 7.54-7.58 (2H, m, C(6)Ar(2)*H* and C(6)Ar(6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.2 (*C*(4)HH), 43.5 (*C*(3)H), 55.5 ($ArOCH_3$), 61.3 ($CO_2CH_2CH_3$), 109.7 (*C*(5)), 114.6 (C(3)Ar*C*(3,5)H), 121.9 (C(6)Ar*C*(3)), 127.5 (C(6)Ar*C*(4)H), 129.2 (C(3)Ar*C*(2,6)H), 129.2 (C(3)Ar*C*(1)), 129.6 (C(6)Ar*C*(5)H), 131.9 (C(6)Ar*C*(5)H), 133.1 (C(6)Ar*C*(2)H), 135.0 (C(6)Ar*C*(1)), 156.8 (*C*(6)), 159.5 (C(3)Ar*C*(4)), 166.0 (CO_2Et), 168.2 (*C*(2)); HRMS (NSI^+) $C_{21}H_{19}Br^{79}O_5Na$ $[M+Na]^+$, found 453.0301, requires 453.0308 (−1.6 ppm).

Ethyl (*R*)-3-(4-methoxyphenyl)-6-(naphthalen-2-yl)-2-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate

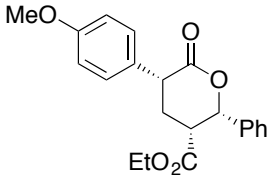


415

Following general procedure M, homoanhydride **676** (140 mg, 0.53 mmol) in CH_2Cl_2 (2 mL), (+)-BTM (5 mg, 0.024 mmol), ethyl 2-(2-naphthoyl)acrylate **393** (100 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) and *i*-Pr_2NEt (93 μL, 0.53 mmol) in CH_2Cl_2 (2 mL) at −78 °C gave crude product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] gave the title compound (116 mg, 77%) as a white solid. mp 88-90 °C; $[\alpha]_D^{20}$ −8.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane:IPA, flow rate 1 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*S*): 24.1 min, t_R(*R*): 28.2 min, 86% ee; ν_{max} (ATR) 2980, 2902 (C-H), 1771 (C=O dihydropyranone), 1695 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 0.94 (3H, t, 7.1, $CO_2CH_2CH_3$), 3.10-3.23 (2H, m, C(4)*H*H and C(4)H*H*), 3.82 (3H, s, $ArOCH_3$), 3.97-4.06 (3H, m, C(3)*H* and $CO_2CH_2CH_3$), 6.95 (2H, d, *J* 8.7, C(3)Ar(3,5)*H*), 7.28 (2H, d, *J* 8.7, C(3)Ar(2,6)*H*), 7.49-7.54 (3H, m, Ar*H*), 7.83-7.86 (3H, m, Ar*H*), 7.99 (1H, s, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 29.5 (*C*(4)HH), 43.7 (*C*(3)H), 55.5 ($ArOCH_3$), 61.2 ($CO_2CH_2CH_3$), 109.1 (*C*(5)), 114.5 (C(3)Ar*C*(3,5)H), 126.0 (C(6)Ar*C*H), 126.6 (C(6)Ar*C*H), 127.4 (C(6)Ar*C*H), 127.5 (C(6)Ar*C*H), 127.8 (C(3)Ar*C*(1)), 127.8 (C(6)Ar*C*H), 128.7 (C(6)Ar*C*H), 128.9 (C(6)Ar*C*H), 129.2 (C(3)Ar*C*(2,6)H), 130.3 (C(6)Ar*C*), 132.6 (C(6)Ar*C*), 134.0 (C(6)Ar*C*(2)), 158.3 (*C*(6)), 159.4 (C(3)Ar*C*(4)), 166.6 (CO_2Et), 168.6 (*C*(2)); HRMS (NSI^+) $C_{25}H_{22}O_5Na$ $[M+Na]^+$, found 425.1355, requires 425.1359 (−1.0 ppm).

9.4.6 Derivatisation of Dihydropyranone 397

Ethyl (2*S*,3*R*,5*R*)-5-(4-methoxyphenyl)-6-oxo-2-phenyltetrahydro-2*H*-pyran-3-carboxylate

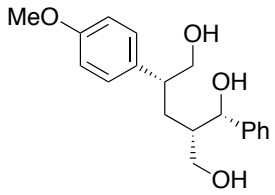


445

To a solution of **397** (150 mg, 0.43 mmol) in EtOAc (11 mL) was added 10% Pd/C (46 mg, 0.043 mmol), a balloon of hydrogen was appended and the reaction stirred at rt for 24 h. Reaction mixture was filtered through celite and concentrated under reduced pressure to give

crude reaction product. Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 70:30 10 CV, 70:30 3 CV)] (hexane:EtOAc 85:15) gave the title compound gave title compound (91 mg, 60% yield) as white solid. mp 128-130 °C; $[\alpha]_D^{20}$ −51.0 (*c* 0.1 CH_2Cl_2); ν_{max} (ATR) 2984, 2979 (C-H), 1769 (C=O dihydropyranone), 1690 (C=O Ester); ^{1}H NMR (300 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.15, $CO_2CH_2CH_3$), 2.37-2.60 (2H, m, C(4)*H*H and C(4)H*H*), 3.39 (1H, ddd, *J* 8.2, 6.0, 4.5, C(3)*H*), 3.82 (3H, s, $ArOCH_3$) 3.84-4.01 (3H, m, C(5)*H* and $CO_2CH_2CH_3$), 5.81 (1H, d, *J* 4.4, C(2)*H*), 6.93 (2H, d, *J* 8.8, C(5)Ar(3,5)*H*), 7.26-7.30 (2H, m, C(5)Ar(2,6)*H*), 7.33-7.40 (5H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H* and C(2)Ar(2,6)*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 13.90 (CO_2CHCH_3), 29.6 (*C*(4)HH), 44.6 (*C*(5)H), 45.7 (*C*(3)*H*), 55.5 ($ArOCH_3$), 61.2 ($CO_2CH_2CH_3$), 78.7 (*C*(2)H), 114.4 (C(5)Ar*C*(3,5)H), 125.9 (C(2)Ar*C*(3,5)H), 128.6 (C(2)Ar*C*(2,6)H), 128.6 (C(2)Ar*C*(4)H), 129.5 (C(5)Ar*C*(1)), 129.9 (C(5)Ar*C*(2,6)H), 136.4 (C(2)Ar*C*(1)), 159.2 (C(5)Ar*C*(4)), 171. 3 (*C*(6)), 172.4 (CO_2Et); HRMS (NSI$^+$) $C_{21}H_{22}O_5Na$ $[M+Na]^+$, found 377.1355, requires 377.1359 (−1.2 ppm).

(1*S*,2*S*,4*R*)-2-(hydroxymethyl)-4-(4-methoxyphenyl)-1-phenylpentane-1,5-diol



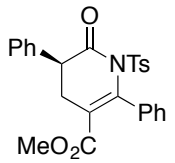
448

To a solution of **445** (42 mg, 0.13 mmol) in anhydrous THF (2 mL), under an N_2 atmosphere, at 0 °C was added dropwise $LiAH_4$ (195 µL, 0.39 mmol, 2 M in THF). The reaction was stirred for 10 min then quenched with aq. HCl (0.1 M). The reaction mixture was extracted with EtOAc (×3) and combined organics dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude reaction product. Purification by Biotage® Isolera™ 4 [SNAP 10 g, 25 mL^{-1}, hexane:EtOAc (100:0 1 CV, 100:0 to 90:10 10 CV, 90:10 3 CV)] gave the title compound (36 mg, 88% yield) as colourless oil. $[\alpha]_D^{20}$ −42.0 (*c* 0.1 CH_2Cl_2); ν_{max} (ATR); 3301 (OH), 2909 (C-H) ^{1}H NMR (500 MHz, $CDCl_3$) 1.59-1.65 (2H, m, C(3)H_2), 2.32 (1H, tt, *J* 10.4, 4.4, C(2)*H*), 2.77 (1H, br. s. O*H*), 2.82-2.87 (1H, m, C(4)*H*), 3.41-3.43 (2H, m, C(2)C(1')H_2), 3.65-3.68 (3H, m, C(5)H_2 and O*H*), 3.80 (3H, s, $ArOCH_3$), 4.25 (1H, br. s, O*H*), 4.94-4.96 (1H, C(1)*H*), 6.89 (2H, d, *J* 8.7, C(4)Ar(3,5)*H*), 7.12 (2H, d, *J* 8.7, C(4)Ar(2,6)*H*), 7.20-7.26 (3H, m, C(1)Ar(3,5)*H* and C(1)Ar(4)*H*), 7.30-7.33 (2H, C(1)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 31.0 (*C*(3)H_2), 43.4 (*C*(2)H), 45.1 (*C*(4)H), 55.4 ($ArOCH_3$), 65.1 (C(2)*C*(1')H_2), 68.0 (*C*(5)H_2), 76.1 (*C*(1)H), 114.4 (C(4)Ar*C*(3,5)H), 125.9 (C(1)Ar*C*(4)H), 127.4 (C(1)Ar*C*(3,5)H), 128.5 (C(1)Ar*C*(2,6)H), 129.0 (C(4)Ar*C*(2,6)H), 133.4 (C(4)Ar*C*(1)), 143.4 (C(1)Ar*C*(1)), 158.7

(C(4)Ar*C*(4)); HRMS (CI$^+$) $C_{19}H_{26}NO_3$ $[M+NH_4]^+$, found 334.2011, requires 334.2013 (−0.6 ppm).

9.4.7 Enantioselective Isothiourea-Catalysed Michael addition-Lactamisation

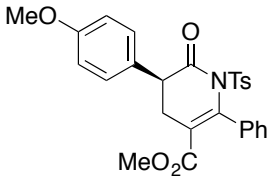
Methyl (*S*)-6-oxo-2,5-diphenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



421

Following general procedure N, phenylacetic acid (37 mg, 0.27 mmol), *i*-Pr_2NEt (70 μL, 0.40 mmol) and pivaloyl chloride (49 μL, 0.40 mmol) in CH_2Cl_2 (3 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (50 mg, 0.13 mmol) and *i*-Pr_2NEt (23 μL, 0.13 mmol) were warmed from −78 °C to rt over 16 h to give crude product. Column chromatography (12:88 EtOAc:Petrol) gave the title compound (44 mg, 72%) as a white solid. mp 172-174 °C; $[\alpha]_D^{20}$ −23.3 (*c* 0.15 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(*S*): 15.8 min, t_R(*R*): 23.0 min, 91% ee; ν_{max} (ATR) 3028, 2955 (C-H), 1711 (C=O dihydropyridone), 1701 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.40 (3H, s, ArC*H*$_3$), 3.01 (1H, dd, *J* 15.2, 5.0, C(4)*H*H), 3.14 (1H, dd, *J* 15.2, 11.5, C(4)H*H*), 3.52 (3H, s, CO_2CH_3), 3.83 (1H, dd, *J* 11.4, 5.0, C(5)*H*), 7.14-7.20 (6H, m, ArC*H*), 7.26-7.40 (6H, m, ArC*H*), 7.47 (2H, d, *J* 8.0, ArC*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (Ar*C*H$_3$), 30.3 (*C*(4)), 51.3 (*C*(5)), 52.0 (CO_2CH_3), 120.7 (*C*(3)), 127.6 (Ar*C*), 128.0 (Ar*C*), 128.2 (Ar*C*), 129.0 (Ar*C*), 129.0 (Ar*C*), 129.1 (Ar*C*), 129.2 (Ar*C*), 129.6 (Ar*C*), 133.9 (4ry Ar*C*), 136.1 (Ar*C*), 136.8 (Ar*C*), 145.1 (Ar*C*), 145.3 (Ar*C*), 166.6 (CO_2CH_3), 173.4 (*C*(6)); HRMS (NSI$^+$) $C_{26}H_{24}NO_5S$ $[M+H]^+$, found 462.1369, requires 462.1370 (−0.2 ppm).

Methyl (*S*)-5-(4-methoxyphenyl)-6-oxo-2-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

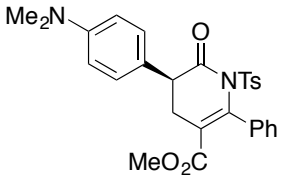


422

Following general procedure N, 4-methoxyphenylacetic acid (45 mg, 0.27 mmol), *i*-Pr_2NEt (70 μL, 0.40 mmol), pivaloyl chloride (49 μL, 0.40 mmol) in CH_2Cl_2 (3 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (50 mg, 0.13 mmol) and *i*-Pr_2NEt (23 μL, 0.13 mmol) were warmed from −78 °C to rt over 16 h to give crude product. Column chromatography

(15:75 EtOAc:Petrol) to give the title compound (50 mg, 76%) as a colourless oil; $[\alpha]_D^{20}$ −31.6 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(*S*): 12.7 min, t_R(*R*): 25.4 min, 95% ee; ν_{max} (ATR) 2951, 2918 (C-H), 1719 (C=O dihydropyridone), 1699 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.39 (3H, s, SO_2ArCH_3), 2.98 (1H, dd, *J* 15.2, 5.0 C(4)*H*H), 3.10 (1H, dd, *J* 15.2, 11.6 C(4)H*H*), 3.52 (3H, s, CO_2CH_3), 3.76-3.79 (4H, m, C(5)*H* and $ArOCH_3$), 6.87 (2H, d, *J* 8.7, C(5)Ar(3,5)*H*), 7.09 (2H, d, *J* 8.7, SO_2Ar(3,5)*H*), 7.14 (2H, d, *J* 8.1, C(2)Ar(3,5)*H*), 7.18-7.19 (2H, m, C(2)Ar(2,6)*H*), 7.28 (2H, d, *J* 7.8, C(5)Ar(2,6)*H*), 7.37 (1H, t, *J* 7.41, C(2)Ar(4)*H*), 7.46 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 30.4 (*C*(4)HH), 50.6 (*C*(5)H), 52.1 (CO_2CH_3), 55.4 ($ArOCH_3$), 114.4 (C(5)Ar*C*(3,5)H), 120.8 (*C*(3)), 127.6 (C(5)Ar*C*(2,6)H), 128.9 (C(5)Ar*C*(1)), 129.1 (SO_2Ar*C*(2,6)H), 129.1 (C(2)Ar*C*(3,5)H), 129.2 (C(2)Ar*C*(4)H), 129.3 (SO_2Ar*C*(3,5)H), 129.6 (C(2)Ar*C*(2,6)H), 133.9 (C(2)Ar*C*(1)), 136.2 (SO_2Ar*C*(4)), 145.1 (*C*(2)), 145.2 (SO_2Ar*C*(1)), 159.2 (C(5)Ar*C*(4)), 166.7 (CO_2Me), 173.7 (*C*(6)); HRMS (NSI^+) $C_{26}H_{24}NO_6S$ $[M+H]^+$, found 492.1466, requires 492.1475 (−1.9 ppm).

Methyl (*S*)-5-(4-(dimethylamino)phenyl)-6-oxo-2-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

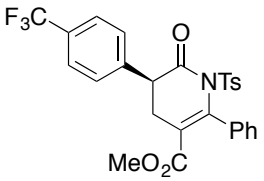


423

Following general procedure N, 4-(dimethylamino)phenyl acetic acid (104 mg, 0.58 mmol), *i*-Pr_2NEt (152 µL, 0.87 mmol), pivaloyl chloride (107 µL, 0.87 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole (4 mg, 0.015 mmol), ketimine **263** (100 mg, 0.29 mmol) and *i*-Pr_2NEt (51 µL, 0.29 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (12:88 EtOAc:Petrol) to give the title compound (100 mg, 68%) as a white solid; mp 164-166 °C : $[\alpha]_D^{20}$ −27.1 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*S*): 23.4 min, t_R(*R*): 26.2 min, 94% ee; ν_{max} (ATR) 2883 (C-H), 1722(C=O dihydropyridinone), 1690 (C=O Ester) 1155 (C-O ester); ^{1}H NMR (400 MHz, $CDCl_3$) 2.39 (3H, s, SO_2ArCH_3), 2.93-3.00 (7H, m, $ArN(CH_3)_2$ and C(4)*H*H), 3.10 (1H, dd, *J* 15.2, 11.3, C(4)H*H*), 3.52 (3H, s, CO_2CH_3), 3.73 (1H, dd, *J* 11.1, 5.0, C(5)*H*), 6.68 (2H, d, *J* 8.6, C(5)Ar(3,5)*H*), 7.03 (2H, *J* 8.59, SO_2Ar(3,5)*H*), 7.13 (2H, d, *J* 8.2, C(2)Ar(3,5)*H*), 7.19 (2H, d, *J* 7.3, C(5)Ar(2,6)*H*), 7.26-7.29 (2H, m, C(2)Ar(3,5)*H*), 7.37 (1H, t, *J* 7.32, C(2)Ar(4)*H*), 7.47 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 30.3 (*C*(4)HH), 40.7 ($ArN(CH_3)_2$), 50.5 (*C*(5)H), 52.0 (CO_2CH_3), 112.9 (C(5)Ar*C*(3,5)H), 120.9

(*C*(3)), 124.3 (C(5)Ar*C*(1)), 127.6 (C(2)Ar*C*(3,5)H), 128.8 (SO_2Ar*C*(3,5)H), 129.0 (C(2)Ar*C*(4)H), 129.1 (C(2)Ar*C*(3,5)H), 129.1 (SO_2Ar*C*(2,6)H), 129.5 (C(5)Ar*C*(2,6)H), 134.1 (SO_2Ar*C*(4)), 136.3 (C(2)*C*(1)), 145.0 (*C*(2)), 145.1 (SO_2Ar*C*(1)), 150.2 (C(5)Ar*C*(4)NMe_2), 166.8 (*C*O_2Me), 174.0 (*C*(6)); HRMS (NSI^+) $C_{28}H_{29}N_2O_5S$ $[M+H]^+$, found 505.1780, requires 505.1792 (−2.3 ppm).

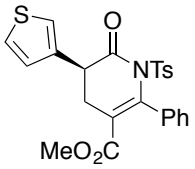
Methyl (*S*)-6-oxo-2-phenyl-1-tosyl-5-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate



424

Following general procedure N, phenylacetic acid (45 mg, 0.27 mmol), *i*-Pr_2NEt (70 μL, 0.40 mmol), pivaloyl chloride (49 μL, 0.40 mmol) in CH_2Cl_2 (3 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (50 mg, 0.13 mmol) and *i*-Pr_2NEt (23 μL, 0.13 mmol) were warmed from −78 °C to rt over 16 h to give crude product. Column chromatography (15:75 EtOAc:Petrol) to give the title compound (50 mg, 76%) as a white solid: mp 138-140 °C; $[\alpha]_D^{20}$ −66.0 (*c* 0.10 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(*R*): 17.2 min, t_R(*S*): 21.5 min, 97% ee; ν_{max} (ATR) 2957, 2930 (C-H), 1730 (C=O dihydropyridone), 1721 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.40 (3H, s, SO_2ArC*H*$_3$), 3.02 (1H, dd, *J* 15.2, 5.0 C(4)*H*H), 3.14 (1H, dd, *J* 15.1, 12.1 C(4)H*H*), 3.53 (3H, s, CO_2C*H*$_3$), 3.89 (1H, dd, *J* 11.9, 4.9, C(5)*H*), 7.15 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.19 (2H, d, *J* 7.4, C(5)Ar(2,6)*H*), 7.26-7.32 (4H, m, C(2)Ar(3,5)*H* and C(2)Ar(2,6)*H*), 7.39 (1H, t, *J* 7.4, C(2)Ar(4)*H*), 7.45 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 7.61 (2H, d, *J* 8.0, C(5)Ar(3,5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8 (SO_2Ar*C*H$_3$), 30.2 (*C*(4)HH), 51.2 (*C*(5)H), 52.1 (CO_2*C*H$_3$), 120.5 (*C*(3)), 124.0 (q, $^1J_{CF}$ 271, Ar*C*F$_3$), 125.9 (q, $^3J_{CF}$ 2.75, C(5)Ar*C*(3,5)H), 127.7 (C(2)Ar*C*(3,5)H), 128.8 (C(2)Ar*C*(2,6)H), 129.1 (SO_2Ar*C*(2,6)H), 129.2 (C(5)Ar*C*(2,6)H), 129.3 (C(2)Ar*C*(4)H), 129.6 (SO_2Ar*C*(3,5)H), 130.3 (q, $^2J_{CF}$ 32.3, C(5)Ar*C*(4)), 133.7 (C(2)Ar*C*(1)), 136.0 (SO_2Ar*C*(4)), 140.8 (C(5)Ar*C*(1)), 145.4 (*C*(2)), 145.6 (SO_2Ar*C*(1)), 166.4 (*C*O_2Me), 172.7 (*C*(6)); ^{19}F NMR (470 MHz) −62.8 (ArC*F*$_3$); HRMS (NSI^+) $C_{27}H_{23}NO_5F_3S$ $[M+H]^+$, found 530.1235, requires 530.1244 (−1.6 ppm).

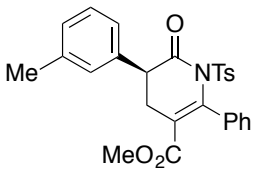
Methyl (*S*)-6-oxo-2-phenyl-5-(thiophen-3-yl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



425

Following general procedure N, 3-thiophene acetic acid (57 mg, 0.40 mmol), *i*-Pr_2NEt (105 μL, 0.60 mmol), pivaloyl chloride (74 μL, 0.60 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (75 mg, 0.20 mmol) and *i*-Pr_2NEt (35 μL, 0.20 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (10:90 EtOAc:Petrol) to give the title compound (61 mg, 65%) as a white solid: mp 159-152 °C; $[\alpha]_D^{20}$ −28.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak IB (92.5:7.5 hexane:IPA, flow rate 1.5 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*S*): 13.9 min, t_R(*R*): 15.8 min, 91% ee; ν_{max} (ATR) 3096, 2957 (C-H), 1720 (C=O dihydropyridone), 1699 (C=O Ester) 1150 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) 2.39 (3H, s, SO_2ArCH_3), 3.05-3.16 (2H, m, C(4)*H*H and C(4)H*H*), 3.52 (3H, s, CO_2CH_3), 4.00 (1H, dd, *J* 8.6, 5.6, C(5)*H*), 6.98 (1H, dd, *J* 5.0, 1.3, C(5)Ar(4)*H*), 7.12-7.15 (5H, m, SO_2Ar(3,5)*H* and C(2)Ar(3,5)*H* and C(5)Ar(2)*H*), 7.24-7.27 (2H, m, C(2)Ar(2,6)*H*), 7.30 (1H, dd, *J* C(5)Ar(5)*H*), 7.36 (1H, tt, *J* 6.8, 1.2, C(2)Ar(4)*H*), 7.45 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2ArCH_3), 29.3 (*C*(4)HH), 46.6 (*C*(5)H), 52.1 (CO_2CH_3), 120.1 (*C*(3)), 122.8 (C(5)Ar*C*(2)H), 126.6 (C(5)Ar*C*(5)H), 127.1 (C(5)Ar*C*(4)H), 127.6 (C(2)Ar*C*(2,6)H), 129.0 (SO_2Ar*C*(2,6)H), 129.1 (C(2)Ar*C*(4)H), 129.2 (SO_2Ar*C*(3,5)H), 129.6 (C(2)Ar*C*(3,5)H), 133.9 (SO_2Ar*C*(4)), 136.1 (C(2)Ar*C*(1)), 136.2 (C(5)*C*(3)), 145.2 (*C*(2)), 145.2 (SO_2Ar*C*(1)), 166.7 (*C*O_2Me), 172.4 (*C*(6)); HRMS (NSI^+) $C_{24}H_{21}NO_5S_2Na$ $[M+Na]^+$, found 490.0739, requires 490.0753 (−2.9 ppm).

Methyl (*S*)-6-oxo-2-phenyl-5-(*m*-tolyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

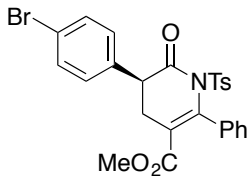


426

Following general procedure N, *m*-tolylacetic acid (40 mg, 0.27 mmol), *i*-Pr_2NEt (70 μL, 0.40 mmol), pivaloyl chloride (49 μL, 0.40 mmol), in CH_2Cl_2 (3 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (50 mg, 0.13 mmol) and *i*-Pr_2NEt (23 μL, 0.13 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (12.5:87.5 EtOAc:Petrol)

to give the title compound (44 mg, 69%) as a colourless oil; $[\alpha]_D^{20}$ −32.1 (*c* 0.10 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S*): 14.7 min, t_R(*R*): 28.7 min, 95% ee; ν_{max} (ATR) 2953 (C-H), 1717 (C=O dihydropyridinone), 1703 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.32 (3H, s, C(5)ArC*H*$_3$), 2.40 (3H, s, SO_2ArC*H*$_3$), 2.98 (1H, dd, *J* 15.2, 5.0 C(4)*H*H), 3.12 (1H, dd, *J* 15.2, 11.8 C(4)H*H*), 3.52 (3H, s, CO_2C*H*$_3$), 3.78 (1H, dd, *J* 11.7, 5.0, C(5)*H*), 6.93-6.97 (2H, m, C(5)Ar(2)*H* and C(5)Ar(4)*H*), 7.10 (1H, d, *J* 7.6, C(5)Ar(6)*H*), 7.16 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.20-7.24 (3H, m, C(5)Ar(5)*H* and C(2)Ar(3,5)*H*), 7.27-7.30 (2H, m, C(2)Ar(2,6)*H*), 7.38 (1H, t, *J* 7.4, C(2)Ar(4)*H*), 7.50 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (C(5)Ar*C*H$_3$), 21.8 (SO_2Ar*C*H$_3$), 30.4 (*C*(4)HH), 51.3 (*C*(5)H), 52.0 (CO_2*C*H$_3$), 120.7 (*C*(3)), 125.3 (C(5)Ar*C*(2)H), 127.6 (C(2)Ar*C*(2,6)H), 128.8 (C(5)Ar*C*(4)H), 128.9 (C(5)Ar*C*(6)H), 128.9 (C(5)Ar*C*(5)H), 129.1 (SO_2Ar*C*(2,6)H), 129.1 (C(2)Ar*C*(4)H), 129.2 (SO_2Ar*C*(3,5)H), 129.5 (C(2)Ar*C*(3,5)H), 134.0 (C(5)Ar*C*(3)), 136.2 (SO_2Ar*C*(4)), 136.8 (C(2)Ar*C*(1)), 138.6 (C(5)Ar*C*(1)), 145.1 (*C*(2)), 145.3 (SO_2Ar*C*(1)), 166.7 (*C*O_2Me), 173.5 (*C*(6)); HRMS (NSI$^+$) $C_{27}H_{26}NO_5S$ $[M+H]^+$, found 476.1517, requires 476.1526 (−1.9 ppm).

Methyl (*S*)-5-(4-bromophenyl)-6-oxo-2-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

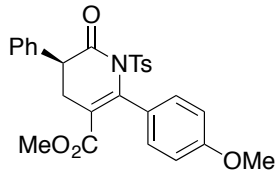


427

Following general procedure N, 4-bromophenylacetic acid (86 mg, 0.40 mmol), *i*-Pr_2NEt (105 µL, 0.60 mmol), pivaloyl chloride (74 µL, 0.60 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.013 mmol), ketimine **263** (75 mg, 0.20 mmol) and *i*-Pr_2NEt (35 µL, 0.20 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (10:90 EtOAc:Petrol) to give the title compound (44 mg, 69%) as a white solid: mp 136-138 °C; $[\alpha]_D^{20}$ −12.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 23.3 min, t_R(*S*): 28.3 min, 72% ee; ν_{max} (ATR) 2949 (C-H), 1730 (C=O dihydropyridinone), 1730 (C=O Ester) 1138 (C-O ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.40 (3H, s, SO_2ArC*H*$_3$), 2.99 (1H, dd, *J* 15.2, 5.1 C(4)*H*H), 3.09 (1H, dd, *J* 15.2, 11.7 C(4)H*H*), 3.52 (3H, s, CO_2C*H*$_3$), 3.78 (1H, dd, *J* 11.7, 5.1, C(5)*H*), 7.05 (2H, d, *J* 8.4, C(5)Ar(2,5)*H*), 7.15 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.18 (2H, d, *J* 7.2, C(2)Ar(3,5)*H*), 7.29 (2H, d, *J* 7.9, C(2)Ar(2,6)*H*), 7.38 (1H, t, *J* 7.5, C(2)Ar(4)*H*), 7.44-7.48 (4H, m, SO_2Ar(2,6)*H* and C(5)Ar(3,5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.8 (SO_2Ar*C*H$_3$), 30.1 (*C*(4)HH), 50.9 (*C*(5)H),

52.1 (CO_2CH_3), 120.5 (*C*(3)), 122.1 (C(5)Ar*C*(4)Br), 127.6 (C(2)Ar*C*(2,6)H), 129.1 (SO_2Ar*C*(2,6)H), 129.2 (SO_2Ar*C*(3,5)H), 129.2 (C(2)Ar*C*(4)H), 129.6 (C(2)Ar*C*(3,5)H), 130.0 (C(5)Ar*C*(3,5)H), 132.2 (C(5)Ar*C*(3,5)H), 133.7 (SO_2Ar*C*(4)), 135.8 (C(2)Ar*C*(1)), 136.0 (C(5)Ar*C*(1)), 145.3 (*C*(2)), 145.4 (SO_2Ar*C*(1)), 166.5 (*C*O_2Me), 172.9 (*C*(6)); HRMS (NSI^+) $C_{26}H_{22}Br^{79}O_5SNa$ $[M+Na]^+$, found 562.0283, requires 562.0294 (−2.0 ppm).

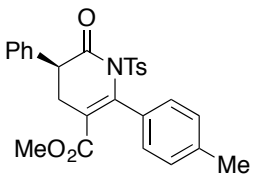
Methyl (*S*)-2-(4-methoxyphenyl)-6-oxo-5-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



428

Following general procedure N, phenylacetic acid (74 mg, 0.54 mmol), *i*-Pr_2NEt (141 μL, 0.81 mmol), pivaloyl chloride (100 μL, 0.81 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.014 mmol), ketimine **267** (100 mg, 0.27 mmol) and *i*-Pr_2NEt (47 μL, 0.27 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (12.5:87.5 EtOAc:Petrol) to give the title compound (44 mg, 69%) as a colourless oil: $[\alpha]_D^{20}$ −16.0 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*S*): 15.5 min, t_R(*R*): 25.8 min, 98% ee; ν_{max} (ATR) 3001 (C-H), 1727 (C=O dihydropyridone), 1705 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.40 (3H, s, SO_2ArCH_3), 2.99 (1H, dd, *J* 15.2, 5.0 C(4)*H*H), 3.10 (1H, dd, *J* 15.2, 11.6 C(4)H*H*), 3.55 (3H, s, CO_2CH_3), 3.80 (1H, dd, *J* 11.5, 5.0, C(5)*H*), 3.85 (3H, s, $ArOCH_3$), 6.80 (2H, d, *J* 8.8, C(2)Ar(3,5)*H*), 7.12-7.18 (6H, m, SO_2Ar(3,5)*H*, C(5)Ar(3,5)*H* and C(5)Ar(2,6)*H*), 7.28-7.34 (3H, m, C(2)Ar(2,6)*H* and C(5)Ar(4)*H*), 7.54 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 21.8 (SO_2ArCH_3), 30.4 (*C*(4)HH), 51.6 (*C*(5)H), 52.1 (CO_2CH_3), 55.4 ($ArOCH_3$), 113.1 (C(2)Ar*C*(3,5)), 119.9 (*C*(3)), 126.3 (C(2)Ar*C*(1)), 128.0 (C(5)Ar*C*(4)H), 128.3 (C(5)Ar*C*(3,5)H), 129.0 (SO_2Ar*C*(2,6)H), 129.1 (C(5)Ar*C*(2,6)H), 129.2 (C(2)Ar*C*(2,6)H), 131.0 (SO_2Ar*C*(3,5)H), 136.4 (SO_2Ar*C*(4)), 137.0 (C(5)Ar*C*(1)), 145.1 (*C*(2)), 145.5 (SO_2Ar*C*(1)), 160.3 (C(2)Ar*C*(4)), 166.8 (*C*O_2Me), 173.5 (*C*(6)); HRMS (NSI^+) $C_{27}H_{26}NO_6S$ $[M+H]^+$, found 492.1467, requires 492.1475 (−1.7 ppm).

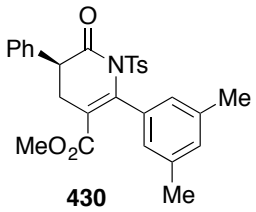
Methyl (*S*)-6-oxo-5-phenyl-2-(*p*-tolyl)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



429

Following general procedure N, phenylacetic acid (76 mg, 0.56 mmol), *i*-Pr_2NEt (146 μL, 0.84 mmol), pivaloyl chloride (103 μL, 0.84 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.014 mmol), methyl 2-((4-methylphenyl)(tosylimino)methyl)acrylate **286** (100 mg, 0.28 mmol) and *i*-Pr_2NEt (49 μL, 0.28 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (15:85 EtOAc:Petrol) to give the title compound (79 mg, 59%) as a white solid: mp 134-136 °C; $[\alpha]_D^{20}$ −14.8 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) $t_R(R)$: 13.3 min, $t_R(S)$: 25.6 min, 90% ee; ν_{max} (ATR) 3032, 2953 (C-H), 1738 (C=O dihydropyridinone), 1717 (C=O Ester); ^{1}H NMR (500 MHz, $CDCl_3$) 2.56 (3H, s, SO_2ArCH_3), 2.57 (3H, s, C(2)ArCH_3), 3.15 (1H, dd, *J* 15.2, 5.0 C(4)*H*H), 3.27 (1H, dd, *J* 15.2, 11.6 C(4)H*H*), 3.71 (3H, s, CO_2CH_3), 3.97 (1H, dd, *J* 11.5, 5.0, C(5)*H*), 7.26-7.33 (6H, m, $SO_2Ar(3,5)H$ and C(2)Ar(3,5)*H*), 7.42-7.51 (5H, m, C(5)Ar(3,5)*H* and C(5)Ar(2,6)*H* and C(5)Ar(5)*H*), 7.68 (2H, d, *J* 8.4, $SO_2Ar(2,6)H$); ^{13}C NMR (125 MHz, $CDCl_3$) 21.7 (C(2)ArCH_3), 21.8 (SO_2ArCH_3), 30.4 (*C*(4)HH), 51.4 (*C*(5)H), 52.1 (CO_2CH_3), 120.2 (*C*(3)), 128.0 (C(5)Ar*C*(4)H), 128.3 (C(2)Ar*C*(3,5)H), 128.4 ($SO_2ArC(3,5)H$), 129.0 (C(5)Ar*C*(3,5)H), 129.1 ($SO_2ArC(2,6)H$), 129.2 (C(2)Ar*C*(2,6)H), 129.4 (C(5)Ar*C*(2,6)H), 131.1 (C(2)Ar*C*(1)), 136.3 ($SO_2ArC(4)$), 136.9 (C(2)Ar*C*(4)), 139.2 (C(5)Ar*C*(1)), 145.1 (*C*(2)), 145.6 ($SO_2ArC(1)$), 166.7 (CO_2Me), 173.4 (*C*(6)); HRMS (NSI^+) $C_{27}H_{25}NO_5SNa$ $[M+Na]^+$, found 498.1338, requires 498.1346 (−1.5 ppm).

Methyl (*S*)-2-(3,5-dimethylphenyl)-6-oxo-5-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate

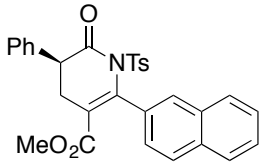


430

Following general procedure N, phenylacetic acid (74 mg, 0.54 mmol), *i*-Pr_2NEt (141 μL, 0.81 mmol), pivaloyl chloride (100 μL, 0.81 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.014 mmol), ketimine **285** (100 mg, 0.27 mmol) and *i*-Pr_2NEt (47 μL, 0.27 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (10:90 EtOAc:Petrol) to give the title compound (44 mg, 69%) as a white solid: mp 182-184 °C; $[\alpha]_D^{20}$ −15.0 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) $t_R(R)$: 11.8 min, $t_R(S)$: 17.6 min, 97% ee; ν_{max} (ATR) 2950 (C-H), 1730 (C=O dihydropyridone), 1700 (C=O Ester) 1150 (C-O ester); ^{1}H NMR (400 MHz, $CDCl_3$) 2.22 (6H, s, C(2)Ar(3,5)C*H*$_3$) 2.40 (3H, s, SO_2ArCH_3), 2.96 (1H, dd, *J* 15.2, 5.1 C(4)*H*H), 3.12

(1H, dd, *J* 15.2, 11.9 C(4)H*H*), 3.54 (3H, s, CO_2CH_3), 3.80 (1H, dd, *J* 11.9, 5.0, C(5)*H*), 6.74 (2H, br. s, C(2)Ar(2,6)*H*), 6.98 (1H, br. s, C(2)Ar(4)*H*), 7.14-7.20 (4H, m, SO_2Ar(3,5)*H* and C(5)Ar(3,5)*H*), 7.28-7.37 (3H, m, C(2)Ar(2,6)*H* and C(5)Ar(4)*H*), 7.50 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.3 (C(2)Ar(3,5)CH_3), 21.8 (SO_2ArCH_3), 30.7 (*C*(4)HH), 51.7 (*C*(5)H), 52.0 (CO_2CH_3), 120.4 (*C*(3)), 127.3 (C(2)Ar*C*(2,6)H), 128.0 (C(5)Ar*C*(3,5)H), 128.4 (SO_2Ar*C*(3,5)H), 129.0 (C(5)Ar*C*(4)H), 129.1 (C(5)Ar*C*(2,6)H), 129.1 (SO_2Ar*C*(2,6)H), 130.9 (C(2)Ar*C*(4)H), 133.4 (SO_2Ar*C*(4)), 136.3 (C(5)Ar*C*(1)), 137.0 (C(2)Ar*C*(1)), 137.1 (C(2)Ar*C*(3,5)), 145.0 (*C*(2)), 145.4 (SO_2Ar*C*(1)), 166.9 (CO_2Me), 173.7 (*C*(6)); HRMS (NSI$^+$) $C_{28}H_{26}NO_5SNa$ $[M+Na]^+$, found 512.1488, requires 512.1502 (−2.8 ppm).

Methyl (*S*)-2-(naphthalen-2-yl)-6-oxo-5-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



431

Following general procedure N, phenylacetic acid (68 mg, 0.50 mmol), *i*-Pr_2NEt (131 μL, 0.75 mmol), pivaloyl chloride (93 μL, 0.75 mmol) in CH_2Cl_2 (5 mL), (−)-tetramisole•HCl **47** (3 mg, 0.014 mmol), ketimine **290** (100 mg, 0.25 mmol) and *i*-Pr_2NEt (44 μL, 0.25 mmol) were warmed −78 °C to rt over 16 h to give crude product. Column chromatography (15:85 EtOAc:Petrol) to give the title compound (88 mg, 69%) as a white solid: mp 157-159 °C; $[\alpha]_D^{20}$ +46.0 (*c* 0.25 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R*): 15.3 min, t_R(*S*): 23.7 min, 91% ee; ν_{max} (ATR) 3037, 2952 (C-H), 1735 (C=O dihydropyridone), 1718 (C=O Ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.31 (3H, s, SO_2ArCH_3), 3.08 (1H, dd, *J* 15.2, 5.1 C(4)*H*H), 3.20 (1H, dd, *J* 15.2, 11.6 C(4)H*H*), 3.50 (3H, s, CO_2CH_3), 3.89 (1H, dd, *J* 11.5, 5.1, C(5)*H*), 6.91 (2H, d, *J* 8.1, Ar*H*), 7.22-7.26 (2H, m, Ar*H*), 7.29-7.38 (6H, m, Ar*H*), 7.44-7.55 (4H, m, Ar*H*), 7.80 (1H, d, *J* 8.5, Ar*H*). 7.86 (1H, d, *J* 8.0, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 21.7 (SO_2ArCH_3), 30.5 (*C*(4)HH), 51.6 (*C*(5)H), 52.1 (CO_2CH_3), 120.7 (*C*(3)), 126.3 (Ar*C*H), 127.0 (Ar*C*H), 127.0 (Ar*C*H), 127.9 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (Ar*C*H), 128.1 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*), 128.9 (Ar*C*H), 129.1 (Ar*C*H), 131.4 (Ar*C*), 132.4 (Ar*C*), 133.4 (Ar*C*), 136.2 (Ar*C*), 137.0 (Ar*C*), 145.1 (*C*(2)), 145.7 (SO_2Ar*C*(1)), 166.5 (CO_2Me), 173.5 (*C*(2)); HRMS (NSI$^+$) $C_{30}H_{25}NO_5SNa$ $[M+Na]^+$, found 534.1339, requires 534.1346 (−1.2 ppm).

9.4.8 X-Ray Structure Determination

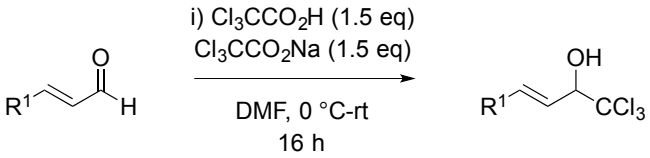
Crystal data for **378**: $C_{24}H_{20}O_4$, M = 372.42, colourless prism, orthorhombic space group *P*21/*c*; *a* = 79008(4) Å, *b* = 9.1343(5) Å, *c* = 25.7027(16) Å, $\alpha = \beta = \gamma = 90°$, *V* = 1854.92(18) Å^3, *Z* = 4, D_c = 1.333 g cm^{-3}, flack parameter = 0.11(4), *R* = 0.0302, R_W = 0.0.0759 for 3354 data with $I > 2\sigma(I)$ and 255 parameters. Data were recorded at 93 K on Rigaku XtaLAB P100 diffractometer using multi-layer mirror monochromated Cu-Kσ radiation and the structures were solved by direct methods and refined using full-matrix least square analysis.

Crystal data for **424**: $C_{27}H_{22}F_3NO_5S$, M = 529.52, colourless prism, orthorhombic space group *P*21/*c*; *a* = 10.1761(10) Å, *b* = 14.7964(15) Å, *c* = 16.1403(17) Å, $\alpha = \beta = \gamma = 90°$, *V* = 2430.2(4) Å^3, *Z* = 4, D_c = 1.447 g cm^{-3}, flack parameter = 0.016(4) *R* = 0.0287, R_W = 0.0759 for 4413 data with $I > 2\sigma(I)$ and 336 parameters. Data were recorded at 93 K on Rigaku XtaLAB P100 diffractometer using multi-layer mirror monochromated Cu-Kσ radiation and the structures were solved by direct methods and refined using full-matrix least square analysis.

9.5 Experimental for Chapter 5

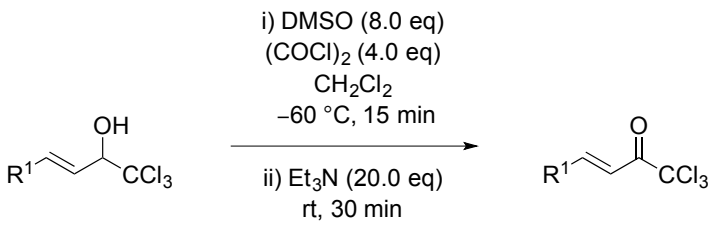
9.5.1 General Experimental Procedures

General Procedure O: *Preparation of trichloromethyl carbinols*



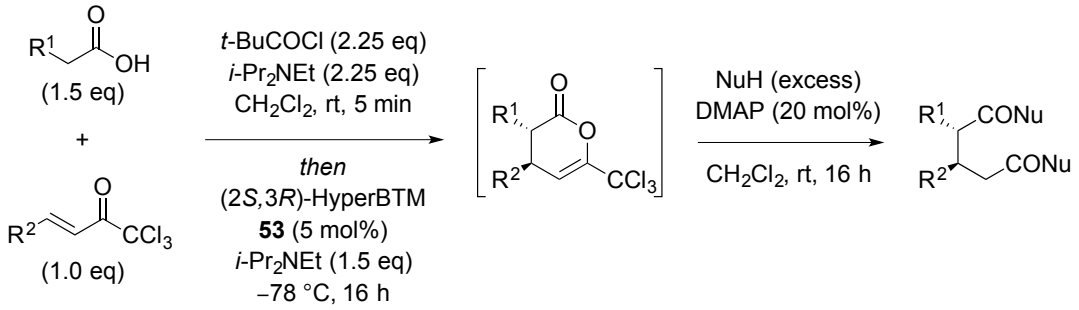
Following a literature procedure,[115] trichloroacetic acid (1.5 eq) and sodium trichloroacetate (1.5 eq) were added to a solution of the appropriate aldehyde (1.0 eq) in DMF at 0 °C. The reaction mixture was stirred in the ice/water bath and allowed to warm slowly to rt over 16 h before being diluted with water and extracted with EtOAc (×3). The combined organic fraction was washed with water (×3), sat. aq. $NaHCO_3$, dried over MgSO4, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography in the solvent system stated.

General Procedure P: *Preparation of α,β-unsaturated trichloromethyl ketones*



Following a literature procedure,[117] a solution of DMSO (8.0 eq) in CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (4.0 eq) in CH_2Cl_2 at −60 °C followed by stirring for 2 min at −60 °C. A solution of the appropriate alcohol (1.0 eq) in CH_2Cl_2 was added dropwise followed by stirring for 15 min at −60 °C. Et_3N (20 eq) was added dropwise and the reaction mixture was stirred and allowed to warm to rt. The reaction mixture was quenched with aq. HCl (2 M) and extracted with CH_2Cl_2 (×3). The combined organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography in the solvent system stated.

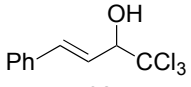
General procedure Q: *Intermolecular Michael addition-lactonisation followed by in situ ring opening*



To a solution of requisite carboxylic acid (1.5 eq) in CH_2Cl_2 (0.1 M in trichloromethyl ketone) were added *i*-Pr_2NEt (2.25 eq) and pivaloyl chloride (2.25 eq) and the reaction mixture was stirred for 5 min before cooling to −78 °C. (2*S*,3*R*)-HyperBTM **53** (5 mol%), the requisite α,β-unsaturated trichloromethyl ketone (1 eq) and *i*-Pr_2NEt (1.5 eq) were added in succession and the reaction mixture was stirred at −78 °C for 16 h. The appropriate nucleophile (excess) and DMAP (20 mol%) were added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with aq. HCl (1 M) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography in the solvent system stated.

9.5.2 Preparation of Trichloromethyl Carbinols

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol



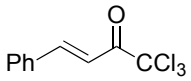
498

Following general procedure O, cinnamaldehyde (5.03 mL, 40.0 mmol), DMF (30 mL), trichloroacetic acid (9.80 g, 60.0 mmol) and sodium trichloroacetate (11.1 g, 60.0 mmol) gave, after column chromatography (Et_2O:Petrol 20:80), the title compound as an orange oil (4.78 g, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) 2.92 (1H, d, *J* 5.6, O*H*), 4.75-4.80 (1H, m, C(2)*H*), 6.37

(1H, dd, *J* 15.9, 6.1, C(3)*H*), 6.91 (1H, d, *J* 15.9, C(4)*H*), 7.28-7.39 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.43-7.47 (2H, m, ArC(2,6)*H*). All spectroscopic data in accordance with the literature.[186]

9.5.3 Preparation of α,β-Unsaturated Trichloromethyl Ketones

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-one

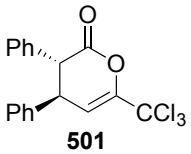


500

Following general procedure P, oxalyl chloride (6.43 mL, 76.0 mmol) in CH_2Cl_2 (300 mL), DMSO (10.8 mL, 152 mmol) in CH_2Cl_2 (35 mL), trichloromethyl carbinol **498** (4.78 g, 19.0 mmol) in CH_2Cl_2 (20 mL) and Et_3N (53.0 mL, 380 mmol) gave, after column chromatography (Et_2O:Petrol 5:95), the title compound (4.41 g, 93%) as a yellow solid; mp 56–58 °C; ν_{max} (ATR) 3059, 3030 (C–H), 1707 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (1H, d, *J* 15.7, C(3)*H*), 7.43-7.49 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.65-7.66 (2H, m, ArC(2,6)*H*), 8.01 (1H, d, *J* 15.7, C(4)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 96.6 (*C*(1)), 115.9 (*C*(3)), 129.1 (Ar*C*), 129.3 (Ar*C*), 131.9 (Ar*C*(4)), 133.9 (Ar*C*(1)), 149.8 (*C*(4)), 180.2 (*C*(2)); HRMS (APCI$^+$) $C_{10}H_8{}^{35}Cl_3O$ $[M+H]^+$, found 248.9634, requires 248.9635 (−0.5 ppm).

9.5.4 Enantioselective Isothiourea-Catalysed Michael Addition-Lactonisation/Ring Opening

(3*R*,4*R*)-3,4-diphenyl-6-(trichloromethyl)-3,4-dihydro-2*H*-pyran-2-one

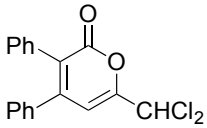


501

Phenyl acetic acid (164 mg, 1.2 mmol), *i*-Pr_2NEt (312 μL, 1.8 mmol), pivaloyl chloride (222 μL, 1.8 mmol), in CH_2Cl_2 (8 mL), (2*S*,3*R*)-HyperBTM **53** (12 mg, 0.04 mmol), trichloromethyl ketone **500** (200 mg, 0.8 mmol), *i*-Pr_2NEt (208 μL, 1.2 mmol) gave crude product (87:13 dr *anti:syn*). Column chromatography (92.5:7.5 Petrol:EtOAc) gave title compound (244 mg, 82%) as a white solid (89:11 *anti:syn*): mp 86-88 °C; ν_{max} (ATR) 1003, 1119, 1454, 1773, 2031, 3063; $[\alpha]_D^{20}$ −98.6 (*c* 0.5 $CHCl_3$); *Data for major anti diastereoisomer:* ^{1}H NMR (500 MHz, $CDCl_3$) 3.97-4.01 (1H, m, C(4)*H*), 4.05-4.07 (1H, m, C(3)*H*), 6.37 (1H, d, *J* 4.1, C(5)*H*), 7.09 (2H, d, *J* 6.7, Ar*H*), 7.16 (2H, d, *J* 6.4, Ar*H*), 7.27-7.35 (6H, m, Ar*H*); ^{1}C NMR (125 MHz, $CDCl_3$) δ_C 45.2 (*C*(3)H), 52.6 (*C*(4)H), 90.1 (*C*Cl_3), 107.8 (*C*(5)H), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 129.0 (Ar*C*H), 129.3 (Ar*C*H), 135.4 (Ar*C*), 139.4 (Ar*C*), 149.0 (Ar*C*), 166.4 (*C*(2)); *Data for minor syn diastereomer;* ^{1}H NMR (500 MHz, $CDCl_3$) δ_H

3.73 (1H, br. s, C(4)*H*), 4.28 (1H, d, *J* 7.0, C(3)*H*), 6.54 (1H, d, *J* 6.0, C(5)*H*), 6.76 (2H, d, *J* 6.8, Ar*H*), 6.81 (2H, d, *J* 6.9, Ar*H*), 7.27-7.35 (6H, m, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 44.6 (*C*(3)H), 50.9 (*C*(4)H), 91.2 (*C*Cl_3), 108.6 (*C*(5)H), 127.2 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*), 129.6 (Ar*C*), 129.8 (Ar*C*H), 149.7 (Ar*C*), 166.1 (*C*(2)); HRMS (NSI$^+$) $C_{18}H_{13}{}^{35}Cl_3O_2Na$ $[M+Na]^+$, found 388.9880, requires 388.9873 (+1.7 ppm). HPLC or GC analysis was not possible in our hands due to the instability of **501**, ee was determined through derivatisation to corresponding diester **507**.

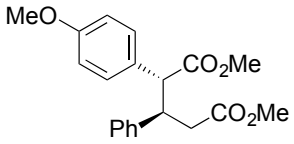
6-(Dichloromethyl)-3,4-diphenyl-2*H*-pyran-2-one



502

To a solution of dihydropyranone **501** (81 mg, 0.22 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at rt was added a solution of MeOH in CH_2Cl_2 (2.4 mL) and reaction stirred for 6 h. Column chromatography (85:15 Petrol: EtOAc) gave the title compound (47 mg, 65%) as a white solid; mp 196-197 °C; ν_{max} (ATR) 1348, 1647, 1709, 3001, 3030, 3090; ^{1}H NMR (500 MHz) 6.40 (1H, s, C*H*Cl_2), 6.73 (1H, s, C(5)*H*), 7.10-7.12 (2H, m, Ar*H*), 7.16 (2H, m, Ar*H*), 7.23-7.30 (6H, m, Ar*H*); ^{13}C NMR (125 MHz) 65.2 (*C*HCl_2), 107.2 (*C*(5)H), 126.2 (*C*(3)), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 129.3 (Ar*C*H), 130.8 (Ar*C*H), 133.1 (Ar*C*(4)), 136.8 (C(3)Ar*C*(1)), 151.2 (C(4)Ar*C*(1)), 155.2 (*C*(2)), 161.2 (C(6)); HRMS (NSI$^+$) $C_{18}H_{13}{}^{35}Cl_2O_2$ $[M+H]^+$, found 331.0296, requires 331.0287 (+2.7 ppm).

Dimethyl (2*R*,3*R*)-2-(4-methoxyphenyl)-3-phenylpentanedioate

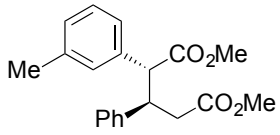


507

Following general procedure Q, 4-methoxyphenylacetic acid (99.7 mg, 0.60 mmol), *i*-Pr_2NEt (156 μL, 0.90 mmol), pivaloyl chloride (111 μL, 0.90 mmol) in CH_2Cl_2 (4 mL), (2*S*,3*R*)-HyperBTM **53** (6 mg, 0.02 mmol), trichloromethyl ketone **500** (100 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol), MeOH (4 mL) and DMAP (10 mg, 0.08 mmol) gave the crude product (92:8 dr). Column chromatography (Et_2O:Petrol 25:75) gave the title compound (105 mg, 77%) as a white solid (>95:5 dr); mp 96-98 °C; {Lit.[187] mp 99-101 °C}; $[\alpha]_D^{20}$ −126.8 (c 0.5 $CHCl_3$); {Lit.[187] $[\alpha]_D^{20}$ −135.1 (*c* 0.2 $CHCl_3$) for >99% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R (2*S*,3*S*):

16.7 min, t_R (2*R*,3*R*): 22.9 min, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 2.73-2.82 (2H, m, C(4)*H*H and C(4)H*H*), 3.51 (3H, s, C(5)O_2C*H*$_3$), 3.69 (3H, s, C*H*$_3$), 3.70 (3H, s, C*H*$_3$), 3.78-3.83 (2H, m, C(2)*H* and C(3)*H*), 6.64-6.68 (2H, m, C(2)ArC(3,5)*H*), 6.99-7.14 (7H, m, ArC*H*). All data in accordance with literature.[187]

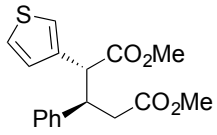
Dimethyl (2*R*,3*R*)-3-phenyl-2-(3-tolyl)pentanedioate



508

Following general procedure Q, *m*-tolylacetic acid (90 mg, 0.6 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol, pivalolyl chloride (111 µL 0.90 mmol), in CH2Cl2 (4 mL), (2*S*,3*R*)-HyperBTM **53** (6 mg, 0.02 mmol), trichloromethyl ketone **500** (100 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) and MeOH (5 mL) gave the crude product (92:8 dr). Column chromatography (EtOAc:Petrol 10:90) gave the title compound (79 mg, 60%) as a white solid (>95:5 dr); mp 72–74 °C {Lit.[187] 73-75 °C}; $[\alpha]_D^{20}$ −135.0 (c 0.1 $CHCl_3$); {Lit.[187] $[\alpha]_D^{20}$−127.4 (c 0.1 $CHCl_3$) for 99% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R (2*S*,3*S*): 8.7 min, t_R (2*R*,3*R*): 10.4 min, 99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) 2.21 (3H, s, ArC*H*$_3$), 2.79-2.84 (2H, m, C(4)*H*H and C(4)H*H*), 3.51 (3H, s, C(5)O_2C*H*$_3$), 3.68 (3H, s, C(1)O_2C*H*$_3$), 3.80–3.88 (2H, m, C(2)*H* and C(3)*H*), 6.90-6.92 (2H, m, Ar*H*), 6.94 (1H, br. s, C(2)Ar(2)*H*), 7.00-7.07 (4H, m, Ar*H*), 7.10-7.13 (2H, m, Ar*H*). All data in accordance with literature.[187]

Dimethyl (2*R*,3*R*)-3-phenyl-2-(thiophen-3-yl)pentanedioate

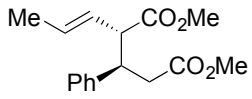


510

Following general procedure Q, 3-thiophene acetic acid (85 mg, 0.6 mmol), *i*-Pr_2NEt (156 µL, 0.90 mmol, pivalolyl chloride (111 µL 0.90 mmol), in CH2Cl2 (4 mL), (2*S*,3*R*)-HyperBTM **53** (6 mg, 0.02 mmol), trichloromethyl ketone **500** (99.8 mg, 0.40 mmol), *i*-Pr_2NEt (104 µL, 0.60 mmol) and MeOH (5 mL) gave the crude product (81:19 dr). Column chromatography (EtOAc:Petrol 10:90) gave the title compound (81 mg, 64%) as a white solid (>98:2 dr); mp 61-64 °C {Lit.[187] 60-64 °C}; $[\alpha]_D^{20}$ −72.0 (*c* 0.5 $CHCl_3$); {Lit.[187] −69.0 (*c* 0.5 $CHCl_3$) for 97% ee (2*R*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:IPA, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R (2*R*,3*R*): 16.9 min, t_R (2*S*,3*S*): 18.3 min, >99% ee; ^{1}H NMR (500

MHz, $CDCl_3$) 2.75-2.83 (2H, m, C(4)*H*H and C(4)H*H*), 3.52 (3H, s, C(5)O_2C*H*$_3$), 3.71 (3H, s, C(1)O_2C*H*$_3$), 3.77-3.82 (1H, m, C(3)H), 4.00 (1H, d, *J* 10.2, C(2)H), 6.85 (1H, dd, *J* 1.1, 5.0, C(2)Ar*H*), 6.91 (1H, dd, *J* 1.0, 2.9, C(2)Ar*H*), 7.00-7.02 (2H, m, C(3)Ar*H*), 7.09-7.12 (2H, m, Ar*H*), 7.14-7.17 (2H, m, Ar*H*). All data in accordance with literature.[187]

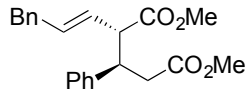
Dimethyl (2*S*,3*R*)-3-phenyl-2-((*E*)-prop-1-en-1-yl)pentanedioate



511

Following general procedure Q, 3-pentenoic acid (61 μL, 0.6 mmol), *i*-Pr_2NEt (156 μL, 0.90 mmol, pivalolyl chloride (111 μL 0.90 mmol), in CH_2Cl_2 (4 mL), (2*S*,3*R*)-HyperBTM **53** (6 mg, 0.02 mmol), trichloromethyl ketone **500** (100 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and MeOH (5 mL) gave the crude product (85:15 dr). Column chromatography (EtOAc:Petrol 10:90) gave the title compound (86 mg, 78%) as a colourless oil (>95:5 dr) $[\alpha]_D^{20}$−67.3 (*c* 0.5 $CHCl_3$); {Lit.[187] $[\alpha]_D^{20}$ −69.0 (*c* 0.5 $CHCl_3$) for >99% ee (2*S*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralpak OD-H (97:3 hexane:IPA, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R (2*R*,3*S*): 9.82 min, t_R (2*S*,3*R*): 15.5 min, >99% ee; ^{1}H NMR (500 MHz, $CDCl_3$) 1.55 (3H, dd, *J* 1.3, 6.3, C(2)C(3′)*H*), 2.69 (2H, d, *J* 7.6, C(4)*H*), 3.27 (1H, d, *J* 8.7, C(3)*H*), 3.52-3.62 (4H, m, C(2)*H* and C(5)O_2C*H*$_3$), 3.67 (C(1)O_2C*H*$_3$), 5.22-5.44 (2H, m, C(2)C(1′)*H* and C(2)C(2′)*H*), 7.09-7.12 (2H, m, C(3)Ar*H*), 7.18-7.29 (3H, m, C(3)Ar*H*). All data in accordance with literature.[187]

Dimethyl (2*S*,3*R*)-3-phenyl-2-((*E*)-3-phenylprop-1-en-1-yl)-pentanedioate



512

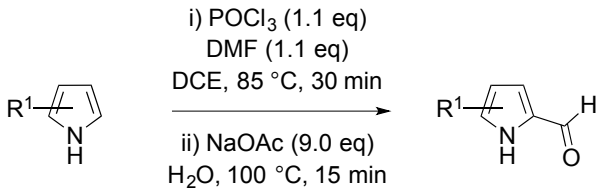
Following general procedure Q, (*E*)-5-phenylpent-3-enoic acid (106 mg, 0.60 mmol), *i*-Pr_2NEt (156 μL, 0.90 mmol), pivaloyl chloride (111 μL, 0.90 mmol) in CH_2Cl_2 (4 mL), (2*S*,3*R*)-HyperBTM **53** (6 mg, 0.02 mmol), trichloromethyl ketone **500** (100 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol), MeOH (4 mL) and DMAP (10 mg, 0.08 mmol) gave the crude product (95:5 dr). Column chromatography (80:20 Petrol:Et_2O) gave the title compound (105 mg, 74%) as a colourless oil (>95:5 dr). $[\alpha]_D^{20}$ −6.7 (*c* 1.0 $CHCl_3$); {Lit.[187] $[\alpha]_D^{20}$ −6.9 (*c* 1.0 $CHCl_3$) for >99% ee (2*S*,3*R*) stereoisomer}; Chiral HPLC analysis, Chiralcel OJ-H (99:1 hexane:IPA, flow rate 1 mL min^{-1}, 211 nm, 40 °C) t_R (2*S*,3*R*): 44.0 min, t_R (2*R*,3*S*): 48.4 min, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 2.69 (2H, d, *J* 7.5, C(4)*H*H and C(4)H*H*), 3.20 (2H, d, *J* 6.3, C(2)C(3′)*H*H and C(2)C(3′)H*H*), 3.33 (1H, t, *J* 9.3, C(2)*H*), 3.53 (3H, s, C(5)O_2C*H*$_3$), 3.57-3.63 (1H, m, C(3)*H*), 3.71 (3H, s, C(1)O_2C*H*$_3$), 5.34 (1H, ddt, *J* 15.3, 9.3, 1.3, C(2)C(1′)*H*), 5.42-5.53 (1H,

m, C(2)C(2′)*H*), 6.75-6.79 (2H, m, ArC*H*), 7.11-7.32 (8H, m, ArC*H*). All data in accordance with literature.[187]

9.6 Experimental for Chapter 6

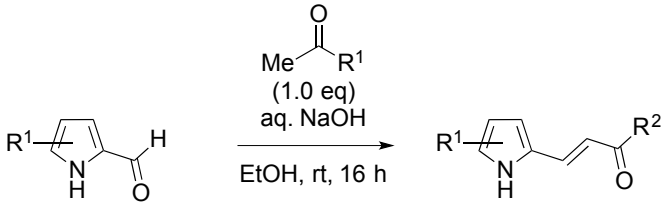
9.6.1 General Experimental Procedures

General procedure R: *Preparation of Pyrrole 2-Carboxaldehydes*



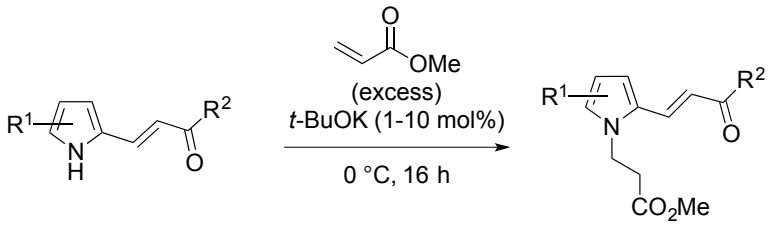
Following literature procedure,[188] $POCl_3$ (1.1 eq) was added dropwise to DMF (1.1 eq) and the reaction was stirred for 15 min at rt. DCE (2.2 M in DMF) was added and the mixture cooled to 0 °C. A solution of requisite pyrrole (1.0 eq) in DCE (2.0 M in pyrrole) was added dropwise and the reaction was heated to 85 °C for 15 min before cooling to rt. A solution of aq. NaOAc (9.0 M, 9.0 eq) was added and the biphasic mixture stirred at 100 °C for 15 min. The reaction was cooled to rt and the phases separated. The aqueous phase was extracted with Et_2O (×3). The combined organics were washed with $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure to provide the desired pyrrole 2-carboxaldehyde.

General Procedure S: *Preparation of Pyrrolyl Enones*



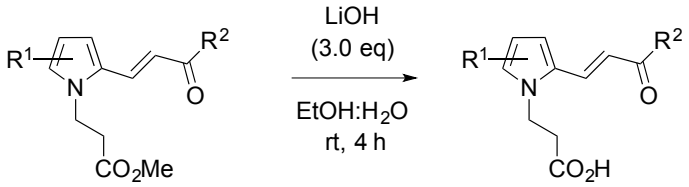
To an aqueous solution of NaOH (10% w/v in H_2O, 2.0 eq) was added dropwise to a solution of pyrrole-2-carboxaldehyde (1.0 eq) and the requisite ketone (1.0 eq) in ethanol (2.5 M in ketone). The reaction was stirred at rt for 16 h then acidified to pH 3 with aqueous HCl (2 M in H_2O). The resultant precipitate was filtered, washed with cold ethanol to provide the desired enone product. Products were purified as described.

General Procedure T: *N-Alkylation of Pyrrolyl Enones*



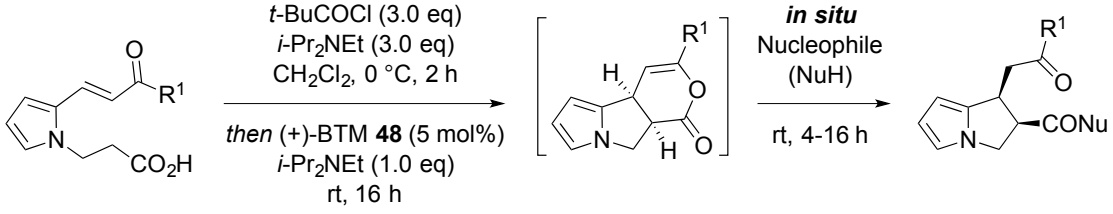
To a solution of pyrrole enone (1.0 eq) in methyl acrylate (0.2 M in pyrrolyl enone) was added potassium *tert*-butoxide (1-10 mol%) and the reaction stirred at 70 °C for 16 h. The reaction was concentrated under reduced pressure, diluted with EtOAc, washed with brine (×3), dried over $MgSO_4$ and concentrated under reduced pressure to provide the crude product. Products were isolated by column chromatography in the solvent system stated.

General Procedure U: *Hydrolysis of Pyrrolyl Enone-Esters*



To a solution of pyrrolyl enone ester (1.0 eq) in H_2O/ethanol (1:1) was added $LiOH.H_2O$ (4.0 eq) and reaction stirred at rt for 4 h. The reaction was then basified to pH 8 with aqueous aq. NaOH (2 M) and washed with Et_2O (×3). The aqueous layer was carefully acidified to pH 3 (caution: acidifying beyond pH 3 can lead to decomposition of product) with aq. HCl (2 M) and extracted with EtOAc (×3). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to provide enone-acid products.

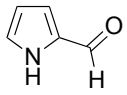
General Procedure V: *Michael Addition-Lactonisation in situ Ring Opening*



To a solution of pyrrolyl enone-acid (1.0 eq) in CH_2Cl_2 (0.1 M) was added pivaloyl chloride (3.0 eq) and *i*-Pr_2NEt (3.0 eq) at 0 °C and the reaction was allowed to warm to rt over 2 h. (+)-BTM **48** (5 mol%) and *i*-Pr_2NEt (1.5 eq) was added and reaction stirred at rt overnight. The requisite nucleophile was then added and the reaction stirred until complete by TLC analysis. Reaction was quenched with aq. HCl (1 M) and extracted with CH_2Cl_2 (×3). Combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to provide crude products. Products were isolated by column chromatography in the solvent system stated.

9.6.2 Synthesis of Pyrrole Aldehydes

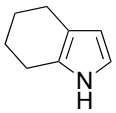
1*H*-Pyrrole 2-carboxaldehyde



552

Following general procedure R, $POCl_3$ (2.0 mL, 21.5 mmol), DMF (1.7 mL, 21.5 mmol) and DCE (10 mL), pyrrole (1.4 mL, 20.2 mmol) in DCE (10 mL) and NaOAc (15 g, 182.9 mmol) in H_2O (20 mL) gave the title compound as a red oil (1.83 g, 96%); ^{1}H NMR (500 MHz, d_6-DMSO) 6.33 (1H, m, pyrrolyl(4)*H*), 7.01 (1H, m, pyrrolyl(3)*H*), 7.18 (1H, m, pyrrolyl(5)*H*), 9.49 (1H, s, C*H*O), 11.13 (1H, br. s, NH). All data in accordance with literature.[189]

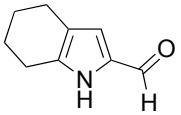
4,5,6,7-Tetrahydro-1*H*-indole



586

Following the literature procedure,[142] $NH_2OH.HCl$ (3.54 g, 50.9 mmol), cyclohexanone (5.28 mL, 50.9 mmol) and KOH (2.86 g, 50.9 mmol) were stirred in DMSO (42 mL) at 70 °C for 30 min. The temperature was increased to 120 °C and further KOH (7.15 g, 127.4 mmol) was added before the slow addition of a solution of DCE (20.5 mL, 259.5 mmol) in DMSO (65 mL) *via* syringe pump over 4 h. The reaction was cooled and added to aq. NH_4Cl (100 mL, 10% in H_2O) and extracted with Et_2O (3×30 mL). The combined organics were washed with aq. KOH (1 M) then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by column chromatography provided the title compound as pink solid (2.19 g, 35%); mp 50-51 °C {Lit.[142] 51-52 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 1.74-1.87 (4H, m, C(5)H_2 and C(6)H_2), 2.57 (4H, dt, *J* 5.8, 20.2, C(4)H_2 and C(7)H_2), 6.00 (1H, br. s, C(3)*H*), 6.64 (1H, t, *J* 2.6, C(2)*H*), 7.70 (1H, N*H*). All data in accordance with literature.[142]

4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde



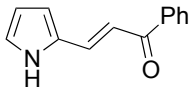
590

Following general procedure R, $POCl_3$ (1.85 mL, 19.9 mmol), DMF (1.54 mL, 19.9 mmol) and DCE (9 mL), 4,5,6,7-tetrahydro-1*H*-indole **586** (1.4 mL, 20.2 mmol) in DCE (9 mL) and NaOAc (13.3 g, 162.3 mmol) in H_2O (18 mL) gave the title compound as a brown oil (2.21 g, 82%); ^{1}H NMR (500 MHz, $CDCl_3$) 1.71-1.83 (4H, m, C(5)H_2 and C(6)H_2), 2.51 (2H, t, *J* 6.1,

(C(4)H_2), 2.67 (2H, t, *J* 6.2, C(7)H_2), 6.73 (1H, s, C(3)*H*), 9.17 (1H, s, C*H*O), 10.5 (1H, br. s, N*H*). All data in accordance with literature.[190]

9.6.3 Synthesis of Pyrrolyl Enones

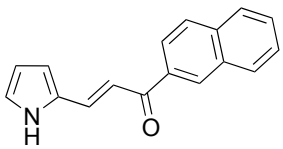
(*E*)-1-phenyl-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



690

Following general procedure S, pyrrole carboxaldehyde (5.00 g, 52.6 mmol), aq. NaOH (5 mL, 10% w/v in H_2O) and acetophenone (6.14 mL, 52.6 mmol) in EtOH (21 mL) gave the title compound as a yellow solid (7.05 g, 68%); mp 135-137 °C; {lit.[190] 136-137 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.34 (1H, s, pyrrolyl(4)*H*), 6.72 (1H, s, pyrrolyl(3)*H*), 7.00 (1H, s, pyrrolyl(5)*H*), 7.20 (1H, d, *J* 15.5, C(2)*H*), 7.47 (2H, m, C(1)Ar(3,5)*H*), 7.33 (1H, m, C(1)Ar(4)*H*), 7.78 (1H, d, *J* 15.5, C(3)*H*), 7.98 (2H, d, *J* 7.3, C(1)Ar(2,6)*H*). All data in accordance with literature.[191]

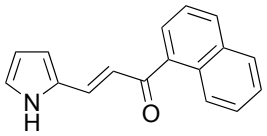
(*E*)-1-(Naphthalen-2-yl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



691

Following general procedure S, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H_2O) and 2-acetylnaphthalene (5.36 g, 31.5 mmol) in EtOH (20 mL) gave the title compound as a yellow solid (5.92 g, 76%); mp 158-160 °C; ν_{max} (ATR)/cm^{-1} 820, 974, 1541 (C-O), 3284 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 6.36 (1H, dd, *J* 1.1, 2.5, pyrrolyl(4)*H*), 6.75-6.76 (1H, m, pyrrolyl(3)*H*), 7.02 (1H, td, 1.4, 2.7, pyrrolyl(5)*H*), 7.30 (1H, d, *J* 15.5, C(2)*H*), 7.57 (2H, dddd, *J* 1.4, 6.9, 8.1, 19.5, Ar*H*), 7.80 (1H, d, *J* 15.5, C(3)*H*), 7.88-7.97 (3H, m, Ar*H*), 8.07 (1H, dd, *J* 1.8, 8.6, Ar*H*), 8.49 (1H, s, Ar*H*), 8.91 (1H, br. s, N*H*); ^{13}C NMR (100 MHz) 111.7 (pyrrolyl*C*(4)H), 115.6 (pyrrolyl*C*(3)H), 116.0 (*C*(2)H), 123.2 (pyrrolyl*C*(5)H), 124.7 (Ar*C*H), 126.9 (Ar*C*H), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 129.5 (pyrrolyl*C*(2)), 129.6 (Ar*C*H), 129.6 (Ar*C*H), 132.7 (Ar*C*), 134.5 (Ar*C*), 135.5 (Ar*C*), 136.1 (*C*(3)H), 190.2 (*C*(1)); HRMS (NSI$^+$), $C_{17}H_{14}NO_2$ $[M+H]^+$, requires 248.1068, found 248.1070 (−0.8 ppm).

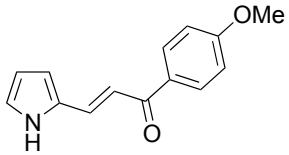
(*E*)-1-(Naphthalen-1-yl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



692

Following general procedure S, pyrrole carboxaldehyde (2.00 g, 21.0 mmol), aq. NaOH (2 mL, 10% w/v in H_2O) and 1-acetylnaphthalene (6.14 mL, 52.6 mmol) in EtOH (8.4 mL) gave the title compound as a yellow oil (1.06 g, 20%); ^{1}H NMR (300 MHz, $CDCl_3$) 6.30-6.33 (1H, m, pyrrolyl(4)*H*), 6.62 (1H, br. s, pyrrolyl(3)*H*), 6.89 (1H, d, *J* 15.9, C(2)*H*), 6.98 (1H, br. s, pyrrolyl(5)*H*), 7.45 (1H, d, *J* 16.0, C(3)*H*), 7.50-7.56 (3H, m, Ar*H*), 7.69 (1H, dd, *J* 1.2, 7.1, Ar*H*), 7.88-7.92 (1H, m, Ar*H*), 7.96-7.99 (1H, m, Ar*H*), 8.23-8.26 (1H, m, Ar*H*), 8.84 (1H, br. s, N*H*); ^{13}C NMR (100 MHz) 111.7 (pyrrolyl*C*(4)H), 116.4 (pyrrolyl*C*(3)H), 121.0 (*C*(2)H), 124.2 (pyrrolyl*C*(5)H), 124.8 (Ar*C*H), 125.8 (Ar*C*H), 126.5 (Ar*C*H), 126.6 (Ar*C*H), 127.3 (Ar*C*H), 128.5 (Ar*C*H), 129.0 (pyrrolyl*C*(2)), 130.6 (Ar*C*), 131.1 (Ar*C*H), 133.9 (Ar*C*), 136.9 (*C*(3)H), 137.7 (Ar*C*), 196.7 (*C*(1)); HRMS (NSI$^+$), $C_{17}H_{14}NO$ $[M+H]^+$, requires 248.1070, found 248.1071 (+0.4 ppm).

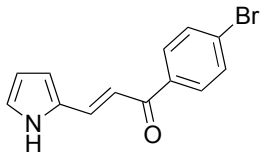
(*E*)-1-(4-methoxyphenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



693

Following general procedure S, pyrrole carboxaldehyde (1.50 g, 15.8 mmol), aq. NaOH (1.5 mL, 10% w/v in H_2O) and 4'-methoxyacetophenone (2.37 g, 15.8 mmol) in EtOH (6.3 mL) gave the title compound as a yellow solid (2.30 g, 64%); mp 164-166 °C; ν_{max} (ATR)/cm^{-1} 1134, 1539 (C-O), 3224 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.88 (3H, s, C(1)ArOC*H*$_3$), 6.33 (1H, br. s, pyrrolyl(4)*H*), 6.71 (1H, s, pyrrolyl(3)*H*), 6.95-6.98 (3H, m, C(1)Ar(3,5)*H* and pyrrolyl(5)*H*), 7.16 (1H, d, *J* 15.5, C(2)*H*), 7.74 (1H, d, *J* 15.5, C(3)*H*), 8.00 (2H, d, *J* 8.8, C(1)Ar(2,6)*H*), 8.85 (1H, s, N*H*); ^{13}C NMR (125 MHz) 55.6 (C(1)ArO*C*H$_3$), 111.6 (pyrrolyl*C*(4)H), 113.9 (C(1)Ar*C*(3,5)H), 114.9 (pyrrolyl*C*(3)H), 115.7 (*C*(2)H), 122.9 (pyrrolyl*C*(5)H), 129.5 (pyrrolyl*C*(2)), 130.7 (C(1)Ar*C*(2,6)H), 131.6 (C(1)Ar*C*(1)), 133.8 (*C*(3)H), 163.3 (C(1)Ar*C*(4)), 188.7 (*C*(1)); HRMS (APCI$^+$), $C_{14}H_{13}NO_2$ $[M+H]^+$, requires 226.0863, found 226.0862 (−0.2 ppm).

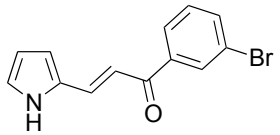
(*E*)-1-(4-bromophenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



694

Following general procedure S, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H_2O) and 4'-bromoacetophenone (6.27 g, 31.5 mmol) in EtOH (13 mL) gave the title compound as a yellow solid (5.48 g, 63%); mp 182-184 °C; ν_{max} (ATR)/cm^{-1} 975, 1330, 1539 (C-O), 3307 (C-H);^{1}H NMR (500 MHz, d_6-DMSO) 6.35 (1H, dt, *J* 2.3, 3.6, pyrrolyl(4)*H*), 6.75 (1H, br. s, pyrrolyl(3)*H*), 7.17 (1H, br. s, pyrrolyl(5)*H*), 7.53 (1H, d, *J* 15.4, C(2)*H*), 7.61 (1H, d, *J* 15.5, C(3)*H*), 7.79 (2H, d, *J* 8.7, C(1)Ar(3,5)*H*), 7.96 (2H, d, *J* 8.6, C(1)Ar(2,6)*H*), 11.74 (1H, s, N*H*); ^{13}C NMR (125 MHz d_6-DMSO) 110.8 (pyrrolyl*C*(4)H), 114.1 (*C*(2)H), 116.8 (pyrrolyl*C*(3)H), 124.6 (pyrrolyl*C*(5)H), 126.6 (pyrrolyl*C*(2)), 129.1 (C(1)Ar*C*(4)), 129.9 (C(1)Ar*C*(3,5)H), 131.8 (C(1)Ar*C*(2,6)H), 134.7 (C(1)Ar*C*(1)), 137.3 (*C*(3)H), 187.3 (*C*(1)); HRMS (APCI$^+$), $C_{13}H_{10}BrNO$ $[M+H]^+$, requires 277.9998, found 277.9999 (+0.2 ppm).

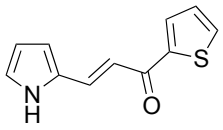
(*E*)-1-(3-bromophenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



695

Following general procedure S, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H_2O) and 3'-bromoacetophenone (4.16 mL, 31.5 mmol) in EtOH (13 mL) gave the title compound as a crude mixture of E/Z isomers (85:15) (5.48 g, 63%). Data for (*E*)-isomer; ^{1}H NMR (500 MHz, d_6-DMSO) 6.21 (1H, m, pyrrolyl(4)*H*), 6.75 (1H, br. s, pyrrolyl(3)*H*), 7.16 (1H, br. s, pyrrolyl(5)*H*), 7.49-7.54 (2H, m, Ar(5)*H* and C(2)*H*), 7.61 (1H, d, *J* 15.3, C(3)*H*), 7.81-7.82 (1H, m, Ar(6)*H*), 7.99-8.00 (1H, m, Ar(4)*H*), 8.14-8.15 (1H, m, Ar(2)*H*), 11.7 (1H, s, N*H*). Due to instability this compound was used immediately without further characterisation.

(*E*)-3-(1*H*-pyrrol-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one

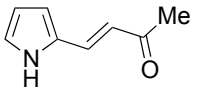


696

Following general procedure S, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H_2O) and 2-acetylthiophene (3.40 mL, 31.5 mmol) in EtOH (13 mL) gave the title compound as a yellow solid (4.55 g, 71%); mp 131-132 °C {Lit.[192] 130 °C}; ^{1}H NMR (500

MHz, $CDCl_3$) 6.34-6.35 (1H, m, pyrrolyl(4)*H*), 6.73 (1H, s, pyrrolyl(3)*H*), 7.00-7.03 (2H, m, C(2)*H* and pyrrolyl(5)*H*), 7.16 (1H, dd, *J* 3.8, 4.9, C(1)Ar(3)*H*), 7.64 (1H, dd, *J* 1.0, 4.9, C(1)Ar(3)*H*), 7.76 (1H, d, *J* 15.4, C(3)*H*), 7.81 (1H, dd, *J* 1.1, 3.8, C(1)Ar(5)*H*). All data in accordance with literature.[192]

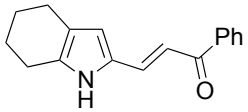
(*E*)-4-(1*H*-Pyrrol-2-yl)but-3-en-2-one



697

Following the procedure from Chimni and Mahajan,[192] to a solution of pyrrole aldehyde (3.00 g, 31.5 mmol) and acetone (23.2 mL, 315.0 mmol) in H_2O (157.5 mL) was added pyrrolidine (0.77 mL, 9.45 mmol) and the reaction stirred at rt for 16 h. The reaction was quenched with HCl (1M in H_2O), extracted with CH_2Cl_2 (×3), dried over $MgSO_4$ and concentrated under reduced pressure to the title compound as a yellow solid (2.97 g, 70%); mp 115-117 °C {Lit.[193] 117-120 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) 2.33 (3H, s, C(1)H_3), 6.30-6.36 (2H, m, C(3)*H* and pyrrolyl(4)*H*), 6.60-6.62 (1H, m, pyrrolyl(3)*H*), 6.98-6.99 (1H, m, pyrrolyl(5)*H*), 7.41 (1H, d, *J* 16.2, C(4)*H*), 8.94 (1H, br. s, N*H*). All data in accordance with literature.[194]

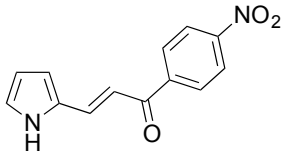
(*E*)-1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-en-1-one



591

Following general procedure S, 4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde **590** (2.21 g, 14.6 mmol), aq. NaOH (3 mL, 10% w/v in H_2O) and acetophenone (1.70 mL, 14.6 mmol) in EtOH (10 mL) gave crude product. The reaction mixture was neutralised to pH 7 with aq. HCl (1 M) and extracted with EtOAc (×3), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane 7.5:92.5) gave the title compound as a brown oil (1.26 g, 34%); ^{1}H NMR (500 MHz, $CDCl_3$) 1.69-1.87 (4H, m, C(3)C(5)H_2 and C(3)C(6)H_2), 2.52 (2H, t, *J* 6.0, (C(3)C(4)H_2), 2.64 (2H, t, *J* 6.1, C(3)C(7)H_2), 6.47 (1H, br. s, C(3)C(3)*H*), 7.01 (1H, d, *J* 15.4, C(3)*H*), 7.43-7.48 (2H, m, C(1)Ar(3,5)*H*), 7.50-7.58 (1H, m, C(1)Ar(4)*H*), 7.68 (1H, d, *J* 15.4, C(2)*H*), 7.95-7.97 (2H, m, C(1)Ar(2,6)*H*), 8.48 (1H, br. s, N*H*). All data in accordance with literature.[194]

(*E*)-1-(4-nitrophenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one

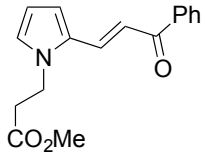


568

Following general procedure S, pyrrole carboxaldehyde (4.79.00 g, 50.4 mmol), aq. NaOH (5 mL, 10% w/v in H_2O) and 4-nitroacetophenone (8.32 g, 50.4 mmol) in EtOH (20 mL) gave the title compound as a black solid (7.93 g, 66%); mp 151-152 °C; ν_{max} (ATR)/cm^{-1} 1514, 1568, 3300 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 6.26 (1H, dt, *J* 2.3, 3.6, pyrrolyl(4)*H*), 6.81 (1H, br. s, pyrrolyl(3)*H*), 7.21 (1H, br. s, pyrrolyl(5)*H*), 7.57 (1H, d, *J* 15.3, C(2)*H*), 7.66 (1H, d, *J* 15.3, C(3)*H*), 8.22 (2H, d, *J* 8.9, Ar(2,6)*H*), 8.39 (2H, d, *J* 8.9, Ar(3,5)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 111.0 (pyrrolyl*C*(3)H), 114.2 (pyrrolyl*C*(4)H), 117.5 (pyrrolyl*C*(5)H), 123.9 (Ar*C*(2,6)H), 125.3 (*C*(2)H), 129.1 (pyrrolyl*C*(2)), 129.2 (Ar*C*(3,5)H), 135.7 (*C*(3)*H*), 143.4 (Ar*C*(1)), 149.5 (Ar*C*(4)), 187.2 (*C*(1)); HRMS (NSI$^+$), $C_{13}H_{11}N_2O_3$ $[M+H]^+$, requires 243.0764, found 243.0762 (−0.9 ppm).

9.6.4 *N*-Alkylation of Pyrrolyl Enones

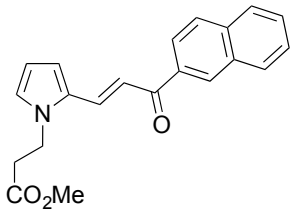
Methyl (*E*)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



699

Following general procedure T, pyrrolyl enone **690** (5.00 g, 25.6 mmol), potassium *tert*-butoxide (29 mg, 0.26 mmol) in methyl acrylate (135 mL) gave the title compound as a yellow oil (6.74 g, 93%); ν_{max} (ATR)/cm^{-1} 1213, 1566, 1583, 1732 (ester C=O), 2951 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.78 (2H, t, *J* 6.9, C(2)H_2), 3.69 (3H, s, CO_2CH_3), 4.39 (2H, t, *J* 6.9, C(3)H_2), 6.23-6.24 (1H, m, pyrrolyl(4)*H*), 6.85-6.86 (1H, m, pyrrolyl(3)*H*), 6.91-6.92 (1H, m, pyrrolyl(5)*H*), 7.33 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.48-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.58 (1H, C(O)Ar(4)*H*), 7.79 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 8.01-8.02 (2H, C(O)Ar(2,6)*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 36.3 (*C*(2)H_2), 42.7 (*C*(3)H_2), 52.2 (CO_2CH_3), 110.4 (pyrrolyl*C*(4)H), 112.8 (pyrrolyl*C*(3)H), 117.2 (pyrrolyl(2)*C*(2)H), 127.2 (pyrrolyl*C*(5)H), 128.4 (C(O)Ar*C*(2,6)H), 128.7 (C(O)Ar*C*(3,5)H), 129.4 (pyrrolyl*C*(2)), 131.7 (pyrrolyl(2)*C*(1)H), 132.6 (C(O)Ar*C*(4)H), 138.8 (C(O)Ar*C*(1)), 171.2 (*C*O_2Me), 189.8 (pyrrolyl(2)*C*(3)); HRMS (NSI$^+$), $C_{17}H_{17}NO_3Na$ $[M+Na]^+$, requires 306.1101, found 306.1094 (−2.2 ppm).

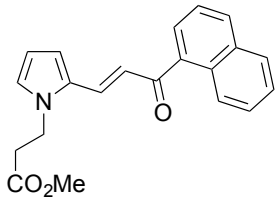
Methyl (*E*)-3-(2-(3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



700

Following general procedure T, pyrrolyl enone **691** (3.00 g, 12.1 mmol), potassium *tert*-butoxide (27 mg, 0.24 mmol) in methyl acrylate (64 mL) gave the title compound as a yellow oil (2.53 g, 63%); ν_{max} (ATR)/cm^{-1} 1170, 1570, 1730 (ester C=O), 2951 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.80 (2H, t, *J* 6.9, C(2)*H*$_2$), 3.69 (3H, s, CO_2CH_3), 4.42 (2H, t, *J* 6.9, C(3)*H*$_2$), 6.25-6.27 (1H, m, pyrrolyl(4)*H*), 6.92-6.94 (2H, m, pyrrolyl(3)*H* and pyrrolyl(5)*H*), 7.49 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.52-7.63 (2H, m, 2×C(O)Ar*H*), 7.82-8.02 (4H, m, pyrrolyl(2)C(1)*H* and 3×C(O)Ar*H*), 8.11 (1H, dd, *J* 1.7, 8.6, C(O)Ar*H*), 8.53 (1H, br. s, C(O)Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 36.3 (*C*(2)H_2), 42.7 (*C*(3)H_2), 52.2 (CO_2CH_3), 110.4 (pyrrolyl*C*(4)H), 112.9 (pyrrolyl*C*(3)H), 117.3 (pyrrolyl(2)*C*(2)H), 124.6 (C(O)Ar*C*H), 126.8 (C(O)Ar*C*H), 127.2 (C(O)Ar*C*H), 127.9 (C(O)Ar*C*H), 128.3 (C(O)Ar*C*H), 128.6 (C(O)Ar*C*H), 129.5 (pyrrolyl*C*(2)), 129.6 (C(O)Ar*C*H), 129.6 (C(O)Ar*C*H), 131.7 (pyrrolyl(2)*C*(1)H), 132.8 (C(O)Ar*C*), 135.5 (C(O)Ar*C*), 136.1 (C(O)Ar*C*(1)), 171.2 (*C*O$_2$Me), 189.6 (pyrrolyl(2)*C*(3)); HRMS (NSI$^+$), $C_{21}H_{19}NO_3Na$ $[M+Na]^+$, requires 356.1257, found 356.1255 (−0.6 ppm).

Methyl (*E*)-3-(2-(3-(naphthalen-1-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate

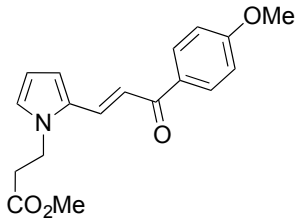


701

Following general procedure T, pyrrolyl enone **692** (1.06 g, 4.47 mmol), potassium *tert*-butoxide (5 mg, 0.043 mmol) in methyl acrylate (22.5 mL) gave the title compound as a yellow oil (922 mg, 62%); ν_{max} (ATR)/cm^{-1} 1280, 1570, 1732 (ester C=O), 2961 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.70 (2H, t, *J* 6.8, C(2)*H*$_2$), 3.65 (3H, s, CO_2CH_3), 4.28 (2H, t, *J* 6.8, C(3)*H*$_2$), 6.21-6.22 (1H, m, pyrrolyl(4)*H*), 6.80 (1H, dd, *J* 1.2, 3.9, pyrrolyl(3)*H*), 6.90 (1H, br. s, pyrrolyl(5)*H*), 7.08 (1H, d, *J* 15.4, pyrrolyl(2)C(2)*H*), 7.50-7.57 (3H, m, Ar*H*), 7.63 (1H, d, *J* 15.4, 7.76-7.77 (1H, m, Ar*H*), 7.89 (1H, d, *J* 8.3, Ar*H*), 7.96 (1H, d, *J* 8.2, Ar*H*), 8.37 (1H, d, *J* 8.2, Ar*H*); ^{13}C NMR (125 MHz) 36.0 (*C*(2)H_2), 42.5 (*C*(3)H_2), 52.0 (CO_2CH_3), 110.4 (pyrrolyl*C*(4)H), 113.3 (pyrrolyl*C*(3)H), 122.0 (pyrrolyl(2)*C*(2)H), 124.6 (C(O)Ar*C*H), 125.8 (C(O)Ar*C*H), 126.4 (C(O)Ar*C*H), 126.8 (C(O)Ar*C*H), 127.2 (C(O)Ar*C*H), 127.5 (C(O)Ar*C*H), 128.4 (C(O)Ar*C*H), 128.8 (pyrrolyl*C*(2)), 130.5 (C(O)Ar*C*), 131.3 (C(O)Ar*C*H), 132.4

(pyrrolyl(2)*C*(1)H), 133.8 (C(O)Ar*C*), 137.9 (C(O)Ar*C*(1)), 170.9 (*C*O_2Me), 194.8 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{21}H_{20}NO_3$ $[M+H]^+$, requires 334.1438, found 334.1439 (+0.3 ppm).

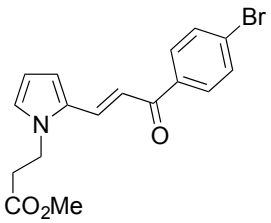
Methyl (*E*)-3-(2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



702

Following general procedure T, pyrrolyl enone **693** (2.00 g, 8.80 mmol), potassium *tert*-butoxide (10 mg, 0.088 mmol) in methyl acrylate (46 mL) gave the title compound as a yellow oil (2.56 g, 97%); ν_{max} (ATR)/cm^{-1} 1168, 1581, 1589, 1732 (ester C=O), 2951 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.78 (2H, t, *J* 6.9, C(2)*H*$_2$), 3.68 (3H, s, CO_2CH_3), 3.88 (3H, s, ArO*CH*$_3$), 4.39 (2H, t, *J* 6.9, C(3)*H*$_2$), 6.21 (1H, m, pyrrolyl(4)*H*), 6.83 (1H, dd, *J* 1.3, 3.9, pyrrolyl(3)*H*), 6.90 (1H, dd, *J* 1.6, 2.5, pyrrolyl(5)*H*), 6.97 (1H, d, *J* 8.9, C(O)Ar(3,5)*H*), 7.34 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.76 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 8.03 (2H, d, *J* 8.9, C(O)Ar(2,6)*H*); ^{13}C NMR (75 MHz) 36.3 (*C*(2)H_2), 42.6 (*C*(3)H_2), 52.1 (CO_2CH_3), 55.6 (ArO*C*H_3), 110.2 (pyrrolyl*C*(4)H), 112.4 (pyrrolyl*C*(3)H), 113.9 (C(O)Ar*C*(3,5)H), 117.2 (pyrrolyl(2)*C*(2)H), 126.9 (pyrrolyl*C*(5)H), 129.5 (pyrrolyl*C*(2)), 130.6 (C(O)Ar*C*(2,6)H), 131.0 (pyrrolyl(2)*C*(1)H), 131.6 (C(O)Ar*C*(1)), 163.3 (C(O)Ar*C*(4)), 171.2 (*C*O_2Me), 188.1 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{18}H_{20}NO_4$ $[M+H]^+$, requires 313.1387, found 313.1379 (−2.6 ppm).

Methyl (*E*)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate

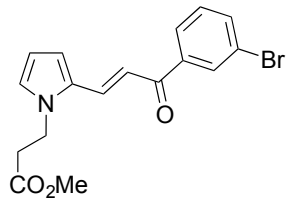


571

Following general procedure T, pyrrolyl enone **694** (3.00 g, 10.9 mmol), potassium *tert*-butoxide (57 mg, 0.26 mmol) in methyl acrylate (57 mL) gave the title compound as a yellow oil (3.51 g, 89%); ν_{max} (ATR)/cm^{-1} 1170, 1678, 1732 (ester C=O), 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.77 (2H, t, *J* 6.9, C(2)*H*$_2$), 3.68 (3H, s, CO_2CH_3), 4.38 (2H, t, *J* 6.9, C(3)*H*$_2$), 6.23 (1H, m, pyrrolyl(4)*H*), 6.86 (1H, dd, *J* 1.1, 4.0, pyrrolyl(3)*H*), 6.92 (1H, dd, *J* 1.6, 2.5, pyrrolyl(5)*H*), 7.26 (1H, d, *J* 15.1, C pyrrolyl(2)C(2)*H*), 7.62 (2H, d, *J* 8.7 C(O)Ar(3,5)*H*), 7.79 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 7.88 (2H, d, *J* 8.7 C(O)Ar(2,6)*H*); ^{13}C NMR (100 MHz,

$CDCl_3$) 36.3 (*C*(2)H_2), 42.6 (CO_2CH_3), 52.2 (*C*(3)H_2), 110.5 (pyrrolyl*C*(4)H), 113.2 (pyrrolyl*C*(3)H), 116.4 (pyrrolyl(2)*C*(2)H), 127.5 (pyrrolyl*C*(5)H), 127.5 (C(O)Ar*C*(4)), 129.3 (pyrrolyl*C*(2)), 129.9 (C(O)Ar*C*(2,6)H), 131.9 (C(O)Ar*C*(3,5)H), 132.1 (pyrrolyl(2)*C*(1)H), 137.5 (C(O)Ar*C*(1)), 171.1 (*C*O_2Me), 188.5 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{17}H_{16}Br^{79}NO_3Na$ $[M+Na]^+$, requires 384.0206, found 384.0207 (+0.3 ppm).

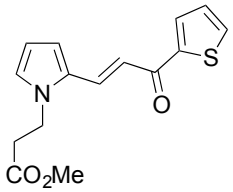
Methyl (*E*)-3-(2-(3-(3-bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



703

Following general procedure T, pyrrolyl enone **695** (3.00 g, 10.9 mmol), potassium *tert*-butoxide (122 mg, 1.09 mmol) in methyl acrylate (57 mL) gave the title compound as a yellow oil (1.62 g, 41%); ν_{max} (ATR)/cm^{-1} 1560, 1578, 1734 (ester C=O), 2953 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.78 (2H, t, *J* 6.9, C(2)H_2), 3.69 (3H, s, CO_2CH_3), 4.40 (2H, t, *J* 6.9, C(3)H_2), 6.24-6.25 (1H, m, pyrrolyl(4)*H*), 6.89 (1H, dd, *J* 1.3, 3.9, pyrrolyl(3)*H*), 6.93-6.94 (1H, m, pyrrolyl(5)*H*), 7.24 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.37 (1H, t, *J* 7.9, C(O)Ar(5)*H*), 7.68 (1H, ddd, *J* 1.0, 1.9, 7.9, C(O)Ar(6)*H*), 7.79 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 7.93 (1H, dt, *J* 1.2, 7.7, C(O)Ar(4)*H*), 8.13 (1H, m, C(O)Ar(2)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 36.3 (*C*(2)H_2), 42.6 (CO_2CH_3), 52.2 (*C*(3)H_2), 110.6 (pyrrolyl*C*(4)H), 113.4 (pyrrolyl*C*(3)H), 116.3 (pyrrolyl(2)*C*(2)H), 123.0 (C(O)Ar*C*(3)), 126.8 (C(O)Ar*C*(4)H), 127.7 (pyrrolyl*C*(5)H), 129.2 (C(O)Ar*C*(2)), 130.3 (C(O)Ar*C*(5)H), 131.4 (C(O)Ar*C*(2)H), 132.4 (pyrrolyl(2)*C*(1)H), 135.4 (C(O)Ar*C*(6)H), 140.6 (C(O)Ar*C*(1)), 171.1 (*C*O_2Me), 188.3 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{17}H_{16}Br^{79}NO_3Na$ $[M+Na]^+$, requires 384.0206, found 384.0201 (−1.2 ppm).

Methyl (*E*)-3-(2-(3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate

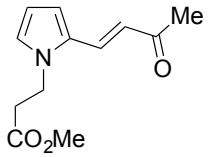


704

Following general procedure T, pyrrolyl enone **696** (3.00 g, 14.8 mmol), potassium *tert*-butoxide (166 mg, 1.48 mmol) in methyl acrylate (78 mL) gave the title compound as a yellow oil (1.28 g, 30%); ν_{max} (ATR)/cm^{-1} 1410, 1570, 1635, 1734 (ester C=O), 2951, 3103 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.77 (2H, t, *J* 6.9, C(2)H_2), 3.69 (3H, s, CO_2CH_3), 4.39 (2H, t, *J* 6.9, C(3)H_2), 6.22-6.24 (1H, m, pyrrolyl(4)*H*), 6.85 (1H, dd, *J* 1.1, 4.0, pyrrolyl(3)*H*), 6.91 (1H, dd,

J 1.6, 2.5, pyrrolyl(5)*H*), 7.15-7.21 (2H, m, C(O)thienyl(4)*H* and pyrrolyl(2)C(2)*H*), 7.64 (1H, dd, *J* 1.1, 5.0, C(O)thienyl(3)*H*), 7.77 (1H, d, *J* 15.0, pyrrolyl(2)C(1)*H*), 7.82 (1H, dd, *J* 1.1, 3.8, C(O)thienyl(5)*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 36.3 (*C*(2)H_2), 42.7 (CO_2CH_3), 52.2 (*C*(3)H_2), 110.4 (pyrrolyl*C*(4)H), 112.9 (pyrrolyl*C*(3)H), 117.0 (pyrrolyl(2)*C*(2)H), 127.3 (pyrrolyl*C*(5)H), 128.3 (C(O)thienyl*C*(5)H), 129.2 (pyrrolyl*C*(2)), 131.0 (pyrrolyl(2)*C*(1)H), 131.2 (C(O)thienyl*C*(4)H), 133.3 (C(O)thienyl*C*(3)H), 146.2 (C(O)thienyl*C*(2)), 171.2 (*C*O_2Me), 181.8 (pyrrolyl(2)*C*(3)); HRMS (NSI$^+$), $C_{15}H_{15}NO_3SNa$ $[M+Na]^+$, requires 312.0665, found 312.0665 (0.0 ppm).

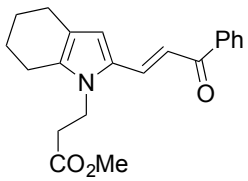
Methyl (*E*)-3-(2-(3-oxobut-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



705

Following general procedure T, pyrrolyl enone **697** (2.97 g, 22.0 mmol), potassium *tert*-butoxide (25 mg, 0.22 mmol) in methyl acrylate (116 mL) gave the title compound as a yellow oil (4.18 g, 90%); ν_{max} (ATR)/cm^{-1} 1174, 1627, 1740 (ester C=O), 2964 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.30 (3H, s, pyrrolyl(2)C(4)*H*$_3$), 2.73 (2H, t, *J* 6.8, C(2)*H*$_2$), 3.66 (3H, s, CO_2CH_3), 4.32 (2H, t, *J* 6.8, C(3)*H*$_2$), 6.18 (1H, ddd, *J* 0.5, 2.7, 3.9, pyrrolyl(4)*H*), 6.50 (1H, d, *J* 15.6, pyrrolyl(2)C(2)*H*), 6.69-6.71 (1H, m, pyrrolyl(3)*H*), 6.86 (1H, dd, *J* 1.7, 2.5, pyrrolyl(5)*H*), 7.44 (1H, d, *J* 15.6, pyrrolyl(2)C(1)*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3 (pyrrolyl(2)*C*(4)H_3) 36.2 (*C*(2)H_2), 42.5 (CO_2CH_3), 52.1 (*C*(3)H_2), 110.3 (pyrrolyl*C*(4)H), 112.7 (pyrrolyl*C*(3)H), 122.0 (pyrrolyl(2)*C*(2)H), 126.9 (pyrrolyl*C*(5)H), 130.2 (pyrrolyl*C*(2)), 171.1 (*C*O_2Me), 197.7 (pyrrolyl(2)*C*(3)); $C_{12}H_{16}NO_3$ $[M+H]^+$, requires 222.1125, found 222.1123 (−0.9 ppm).

Methyl (*E*)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propanoate

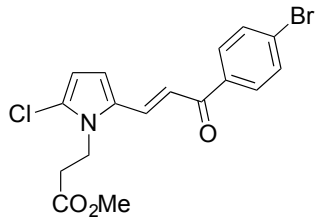


592

Following general procedure T, pyrrolyl enone **591** (1.26 g, 5.01 mmol), potassium *tert*-butoxide (6 mg, 0.05 mmol) in methyl acrylate (26 mL) gave the title compound as a red oil (1.90 g, 95%); ν_{max} (ATR)/cm^{-1} 1549, 1581, 1732 (ester C=O), 2926 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 1.71-1.76 (2H, m, C(3)C(6)*H*$_2$), 1.83-1.88 (2H, m, C(3)C(5)*H*$_2$), 2.52 (2H, m,

C(3)C(4)H_2), 2.61 (2H, t, *J* 6.1, C(3)C(7)H_2), 2.70 (2H, t, *J* 6.5, C(2)H_2), 3.70 (3H, s, CO_2CH_3), 4.27 (2H, t, *J* 6.1, C(3)H_2), 6.69 (1H, s, C(3)pyrrolyl(3)*H*), 7.24 (1H, d, *J* 15.1, C(3)Ar(2)C(2)*H*), 7.46-7.49 (2H, m, C(O)Ar(3,5)*H*), 7.51-7.56 (1H, m, C(O)Ar(4)*H*), 7.79 (1H, d, *J* 15.0, C(3)Ar(2)C(1)*H*), 7.99-8.01 (2H, m, C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 22.6 (C(3)*C*(7)H_2), 23.1 (C(3)*C*(4)H_2), 23.1 (C(3)*C*(5)H_2), 23.4 (C(3)*C*(6)H_2), 36.0 (*C*(2)H_2), 36.9 (*C*(3)H_2), 52.2 (CO_2CH_3), 111.8 (C(3)Ar*C*(3)H), 114.8 (C(3)Ar(2)*C*(2)H), 121.1 (C(3)*C*(4*a*)), 128.3 (C(O)Ar*C*(2,6)H), 128.3 (C(3)Ar*C*(2)), 128.6 (C(O)Ar*C*(3,5)H), 132.0 (C(3)Ar(2)*C*(1)H), 132.3 (C(O)Ar*C*(4)H), 135.6 (C(3)Ar(2)*C*(2)), 139.2 (C(O)*C*(1)), 171.1 (*C*O_2Me), 189.7 (C(3)Ar(2)*C*(3)); HRMS (NSI$^+$), $C_{21}H_{23}NO_3Na$ $[M+Na]^+$, requires 360.1576, found 360.1541 (−9.7 ppm).

Methyl (*E*)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-5-chloro-1*H*-pyrrol-1-yl)propanoate

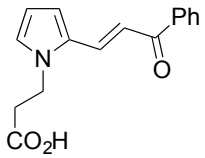


572

To a solution of pyrrolyl enone-ester **571** (2.20 g, 6.08 mmol) in CH_2Cl_2 (87 mL) at 0 °C was added *N*-chlorosuccinimide (975 mg, 7.30 mmol) portionwise. The reaction was allowed to warm to rt and stirred for 4 h. Reaction was quenched with saturated aq. $NaCO_3$, extracted with CH_2Cl_2 (×3), dried over $MgSO_4$ and concentrated under reduced pressure to crude reaction mixture. Column chromatography (EtOAc:hexane 15:85) gave the title compound as a brown oil (600 mg, 25%) ; ν_{max} (ATR)/cm^{-1} 1555, 1587, 1739 (ester C=O), 2998 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.74 (2H, t, *J* 6.9, C(2)H_2), 3.71 (3H, s, CO_2CH_3), 4.42 (2H, t, *J* 6.9, C(3)H_2), 6.21 (1H, d, *J* 4.2, pyrrolyl(4)*H*), 6.83 (1H, d, *J* 4.2, pyrrolyl(3)*H*), 7.26 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.61-7.65 (2H, m, C(O)Ar(3,5)*H*), 7.76 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 7.86-7.90 (2H, m, C(O)Ar(3,5)*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 35.2 (*C*(2)H_2), 39.8 (CO_2CH_3), 52.2 (*C*(3)H_2), 109.7 (pyrrolyl*C*(4)H), 112.6 (pyrrolyl*C*(3)H), 116.5 (pyrrolyl(2)*C*(2)H), 127.8 (), 129.3 (pyrrolyl*C*(2)), 129.9 (C(O)Ar*C*(2,6)H), 132.0 (pyrrolyl(2)*C*(1)H), 132.0 (C(O)Ar*C*(3,5)H), 137.4 (pyrrolyl*C*(5)), 170.6 (*C*O_2Me), 188.4 (pyrrolyl(2)*C*(3)); $C_{17}H_{18}{}^{77}BrClNO_3$ $[M+H]^+$, requires 397.9974, found 397.9970 (−1.1 ppm).

9.6.5 Hydrolysis of Pyrrolyl Enone-Esters

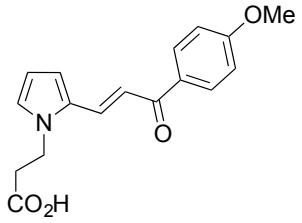
(*E*)-3-(2-(3-Oxo-3-phenylprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid



555

Following general procedure U, pyrrole enone ester **699** (8.00 g, 28.4 mmol) and LiOH (3.57 g, 85.2 mmol) in H_2O/ethanol (105 mL:105 mL) gave the title compound as a brown solid (4.96 g, 65%); mp 103-104 °C; ν_{max} (ATR)/cm^{-1} 1641 (C=O), 1732 (C=O), 3157 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.85 (2H, t, *J* 7.1, C(2)H_2), 4.41 (2H, t, *J* 7.1, C(3)H_2), 6.25-6.26 (1H, m, pyrrolyl(4)*H*), 6.88 (1H, dd, *J* 1.3, 3.9, pyrrolyl(3)*H*), 6.94 (1H, m, pyrrolyl(5)*H*), 7.35 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.48-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.56-7.59 (1H, C(O)Ar(4)*H*), 7.86 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 8.01-8.03 (2H, C(O)Ar(2,6)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 36.1 (*C*(2)H_2), 42.5 (*C*(3)H_2), 52.2 (CO_2CH_3), 110.6 (pyrrolyl*C*(4)H), 113.1 (pyrrolyl*C*(3)H), 116.9 (pyrrolyl(2)*C*(2)H), 127.4 (pyrrolyl*C*(5)H), 128.5 (C(O)Ar*C*(2,6)H), 128.7 (C(O)Ar*C*(3,5)H), 129.5 (pyrrolyl*C*(2)), 132.4 (pyrrolyl(2)*C*(1)H), 132.8 (C(O)Ar*C*(4)H), 138.7 (C(O)Ar*C*(1)), 174.5 (*C*O_2H), 190.3 (pyrrolyl(2)*C*(3)); HRMS (NSI+), $C_{16}H_{15}NO_3Na$ $[M+Na]^+$, requires 292.0944, found 292.0947 (+1.0 ppm).

(*E*)-3-(2-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid

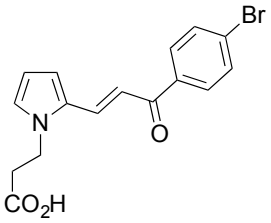


560

Following general procedure U, pyrrole enone ester **702** (2.43 g, 7.75 mmol) and LiOH (978 mg, 23.3 mmol) in H_2O/ethanol (29 mL:29 mL) gave the title compound as a brown solid (1.90 g, 82%); mp 147-148 °C; ν_{max} (ATR)/cm^{-1} 1634 (C=O), 1730, (C=O), 3084 C-H); ^{1}H NMR (500 MHz, d_6-DMSO) 2.69 (2H, t, *J* 6.9, C(2)H_2), 3.86 (3H, s, OCH_3), 4.33 (2H, t, *J* 6.9, C(3)H_2), 6.18-6.20 (1H, m, pyrrolyl(4)*H*), 7.04-7.08 (3H, m, pyrrolyl(3)*H* and C(O)Ar(3,5)*H*), 7.11-7.12 (1H, m, pyrrolyl(5)*H*), 7.56 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.70 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 8.07-8.12 (m, 2H, C(O)ArC(2,6)*H*), 12.38 (1H, br. s., O*H*); ^{13}C NMR (125 MHz, d_6-DMSO) 36.0 (*C*(2)H_2), 42.1 (*C*(3)H_2), 55.5 (O*C*H_3), 109.6 (pyrrolyl*C*(4)H), 112.9 (pyrrolyl*C*(3)H), 113.9 (C(O)Ar*C*(3,5)H), 116.3 (pyrrolyl(2)*C*(2)H), 127.3 (pyrrolyl*C*(5)H), 128.94 (pyrrolyl*C*(2)), 130.5 (C(O)Ar*C*(2,6)H) 131.0 (C(O)Ar*C*(1)), 131.1 (pyrrolyl(2)*C*(1)H),

162.8 (C(O)Ar*C*(1)), 172.0 (*C*(1)), 186.7 (pyrrolylC(2)*C*(3)); HRMS (NSI^+), $C_{17}H_{16}NO_4$ $[M-H]^-$, found 298.1085, requires 298.1081 (−1.3 ppm).

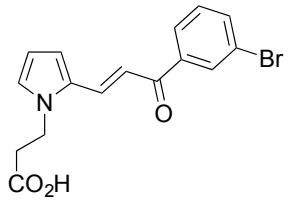
(*E*)-3-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid



561

Following general procedure U, pyrrole enone ester **571** (4.11 g, 11.4 mmol) and LiOH (1.44 g, 34.2 mmol) in H_2O/ethanol (48 mL:48 mL) gave the title compound as a yellow solid (3.57 g, 90%); mp 110-112 °C; ν_{max} (ATR)/cm^{-1} 1636 (C=O), 1726 (C=O), 3059 (C-H); ^{1}H NMR (500 MHz, d_6-DMSO) 2.69 (2H, t, *J* 6.9, C(2)*H*), 4.33 (2H, t, *J* 6.9, C(3)*H*), 6.20-6.22 (1H, m, pyrrolyl(4)*H*), 7.10 (1H, dd, *J* 4.0, 1.5, pyrrolyl(3)*H*), 7.14-7.16 (1H, m, pyrrolyl(5)*H*), 7.54 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.73-7.78 (3H, m, pyrrolyl(2)C(1)*H* and C(O)Ar(3,5)*H*), 8.02-8.06 (2H, m, C(O)Ar(2,6)*H*), 12.4 (1H, br. s., O*H*); ^{13}C NMR (125 MHz, d_6-DMSO) 36.0 (*C*(2)H_2), 42.0 (*C*(3)H_2), 110.0 (pyrrolyl*C*(4)H), 113.6 (pyrrolyl*C*(3)H), 115.7 (pyrrolyl(2)*C*(2)H), 128.0 (C(O)Ar*C*(4)), 130.0 (pyrrolyl*C*(2)), 130.2 (C(O)Ar*C*(2,6)H), 131.7 (C(O)Ar*C*(3,5)H), 132.40 (pyrrolyl(2)*C*(1)H), 137.2 (C(O)Ar*C*(1)), 172.0 (*C*O_2H), 187.3 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{16}H_{15}Br^{79}NO_3$ $[M+H]^+$, requires 348.0230, found 348.0233 (+0.9 ppm).

(*E*)-3-(2-(3-(3-Bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid

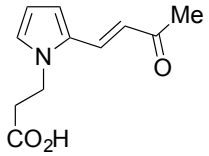


562

Following general procedure U, pyrrole enone ester **703** (1.40 g, 3.87 mmol) and LiOH (487 mg, 11.6 mmol) in H_2O/ethanol (14 mL:14 mL) gave the title compound as a yellow solid (1.07 g, 81%); mp 138-140 °C; ν_{max} (ATR)/cm^{-1} 1584, 1728 (C=O), 3096 (C-H); ^{1}H NMR (400 MHz, d_6-DMSO) 2.69 (2H, t, *J* 6.9, C(2)H_2), 4.33 (2H, t, *J* 6.9, C(3)H_2), 6.21-6.22 (1H, m, pyrrolyl(4)*H*), 7.14-7.16 (2H, m, pyrrolyl(3)*H* and pyrrolyl(5)*H*), 7.50-7.57 (2H, m, pyrroly(2)C(2)*H* and C(O)Ar(5)*H*), 7.77 (1H, d, *J* 15.0, pyrrolyl(2)C(2)*H*), 7.83 (1H, dd, *J* 1.1, 8.0, C(O)Ar(5)*H*), 8.09 (1H, dt, *J* 1.1, 7.8, C(O)Ar(4)*H*), 8.23 (1H, t, *J* 1.8, C(O)Ar(2)*H*); ^{13}C NMR (125 MHz, d_6-DMSO) 36.0 (*C*(2)H), 42.1 (*C*(3)H), 110.0 (pyrrolyl(4)*H*), 113.9 (pyrrolyl(3)*H*), 115.6 (pyrrolyl(2)C(2)*H*), 122.3 (C(O)Ar*C*(3)), 127.2 (C(O)Ar*C*(6)H), 128.2

(C(O)Ar*C*(6)H), 128.9 (C(O)Ar*C*(5)H), 130.6 (CO)Ar*C*(2)H), 130.9 (pyrrolyl*C*(2)), 132.7 (C(O)Ar*C*(4)H), 135.2 (pyrrolyl(2)*C*(1)H), 140.3 (C(O)Ar*C*(1)), 172.0 (*C*O_2H), 186.9 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $C_{16}H_{15}Br^{79}NO_3$ $[M+H]^+$, requires 276.0501, found 276.9886 (+0.9 ppm).

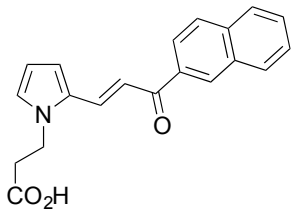
(*E*)-3-(2-(3-Oxobut-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid



563

Following general procedure U, pyrrolyl enone ester **705** (4.41 g, 19.9 mmol) and LiOH (2.51 g, 59.7 mmol) in H_2O/ethanol (74 mL:74 mL) gave the title compound as a brown solid (1.12 g, 92%); mp 122-124 °C; ν_{max} (ATR)/cm^{-1} 1591, 1714 (C=O), 2906 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 2.27 (3H, s, C(O)C*H*$_3$), 2.65 (2H, t, *J* 6.8, C(2)*H*$_2$), 4.30 (2H, d, *J* 6.8 C(3)*H*$_2$), 6.13-6.15 (1H, m, pyrrolyl(4)*H*), 6.45 (1H, d, *J* 15.6, pyrrolyl(2)C(2)*H*), 6.77 (1H, dd, *J* 1.4, 3.9, pyrrolyl(3)*H*), 7.06-7.07 (1H, m, pyrrolyl(5)*H*), 7.53 (1H, d, *J* 15.9, pyrrolyl(2)C(1)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 27.1 (C(O)*C*H$_3$), 36.2 (*C*(2)H$_2$), 42.1 (*C*(3)H$_2$), 109.8 (pyrrolyl*C*(4)H), 112.1 (pyrrolyl*C*(3)H), 122.2 (pyrrolyl(2)*C*(2)H), 127.2 (pyrrolyl*C*(5)H), 128.2 (pyrrolyl*C*(2)), 131.5 (pyrrolyl(2)*C*(1)H), 172.3 (*C*O_2H), 197.5 (pyrrolyl(2)*C*(3)); $C_{11}H_{12}NO_3$ $[M-H]^-$, requires 206.0823, found 206.0823 (0.0 ppm).

(*E*)-3-(2-(3-(Naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid

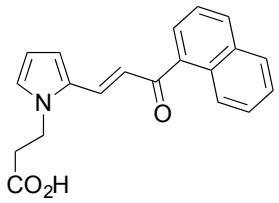


565

Following general procedure U, pyrrolyl enone ester **700** (2.53 g, 7.57 mmol) and LiOH (952 mg, 22.7 mmol) in H_2O/ethanol (28 mL:28 mL) gave the title compound as a brown solid (1.35 g, 56%); mp 120-122 °C; ν_{max} (ATR)/cm^{-1} 1556, 1728 (C=O), 3047 (C-H); ^{1}H NMR (400 MHz, *d*$_6$-DMSO) 2.72 (2H, t, *J* 6.9, C(2)*H*$_2$), 4.36 (2H, t, *J* 6.9, C(3)*H*$_2$), 6.23-6.24 (1H, m, pyrrolyl(4)*H*), 7.12-7.16 (2H, m, pyrrolyl(3)*H* and pyrrolyl(5)*H*), 7.61-7.69 (2H, m, Ar*H*), 7.74 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.81 (1H, d, *J* 15.1, pyrrolyl(2)C(1)*H*), 7.96-8.05 (2H, m, Ar*H*), 8.10-8.16 (2H, m, Ar*H*), 8.83 (1H, s, Ar*H*), 12.4 (1H, br. s, CO_2H); ^{13}C NMR (100 MHz, *d*$_6$-DMSO) 36.0 (*C*(2)H$_2$), 42.1 (*C*(3)H$_2$), 109.8 (pyrrolyl*C*(4)H), 113.3 (pyrrolyl*C*(3)H), 116.3 (pyrrolyl(2)*C*(2)H), 124.2 (C(O)Ar*C*H), 126.9 (C(O)Ar*C*H), 127.7 (C(O)Ar*C*H), 127.7 (C(O)Ar*C*H), 128.3 (C(O)Ar*C*H), 128.4 (pyrrolyl*C*(5)H), 129.0 (C(O)Ar*C*H), 129.5

(C(O)Ar*C*H), 129.6 (pyrrolyl*C*(2)), 131.8 (C(O)Ar*C*), 132.4 (pyrrolyl(2)*C*(1)H), 134.9 (C(O)Ar*C*), 135.5 (C(O)Ar*C*), 172.0 (*C*O_2H), 188.2 (pyrrolyl(2)*C*(3)); HRMS (NSI–), $C_{20}H_{16}NO_3$ $[M-H]^-$, requires 318.1136, found 318.1131 (−1.5 ppm).

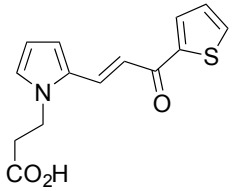
(*E*)-3-(2-(3-(Naphthalen-1-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid



566

Following general procedure U, pyrrolyl enone ester **701** (1.68 g, 5.04 mmol) and LiOH (634 mg, 15.1 mmol) in H_2O/ethanol (19 mL:19 mL) gave the title compound as a crude residue of 80% purity; ^{1}H NMR (400 MHz, d^6-DMSO) 2.65 (2H, t, *J* 6.9, C(2)H_2), 4.24 (2H, t, *J* 6.9, C(3)H_2), 6.18-6.19 (1H, m, pyrrolyl(4)*H*), 6.98-6.98 (1H, m, pyrrolyl(3)*H*), 7.13-7.14 (1H, m, pyrrolyl(5)*H*), 7.17 (1H, d, *J* pyrrolyl(2)C2)*H*), 7.55-7.63 (5H, m, C(O)Ar*H* ×3 and pyrrolyl(2)C(1)*H*), 7.88-7.89 (1H, m, C(O)Ar*H*), 8.02-8.03 (1H, m, C(O)Ar*H*), 8.10-8.11 (1H, m, C(O)Ar*H*), 8.29-8.30 (1H, m, C(O)Ar*H*) 12.3 (1H, br. s, CO_2H). The crude residue was carried forward immediately into the next step without further characterisation.

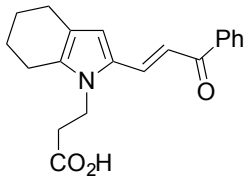
(*E*)-3-(2-(3-oxo-3-(Thiophen-2-yl)prop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoic acid



566

Following general procedure U, pyrrole enone ester **704** (1.28 g, 4.42 mmol) and LiOH (319 mg, 13.3 mmol) in H_2O/ethanol (16 mL:16 mL) gave the title compound as a yellow solid (1.12 g, 92%); mp 122-124 °C; ν_{max} (ATR)/cm^{-1} 1558, 1627 (C=O), 1726 (C=O), 2910 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 2.84 (2H, t, *J* 7.2, C(2)H_2), 4.33 (2H, t, *J* 6.9, C(3)H_2), 6.24-6.26 (1H, dd, *J* 2.7, 3.5, pyrrolyl(4)*H*), 6.88 (1H, dd, *J* 1.2, 4.0, pyrrolyl(3)*H*), 6.94 (1H, dd, 1.6, 2.5, pyrrolyl(5)*H*), 7.16-7.22 (2H, m, pyrrolyl(2)C(2)*H* and C(O)thienyl(4)*H*), 7.66 (1H, dd, *J* 1.1, 4.9, C(O)thienyl(3)*H*), 7.84-7.88 (2H, m, C(O)thienyl(5)*H* and pyrrolyl(2)C(1)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 36.1 (*C*(2)H_2), 42.5 (*C*(3)H_2), 110.7 (pyrrolyl*C*(4)H), 113.1 (pyrrolyl*C*(3)H), 116.8 (pyrrolyl(2)*C*(2)H), 127.5 (pyrrolyl*C*(5)H), 128.4 (C(O)thienyl*C*(4)H), 129.3 (pyrrolyl*C*(2)), 131.6 (C(O)thienyl*C*(5)H), 131.7 (pyrrolyl(2)*C*(1)H), 133.7 (C(O)thienyl*C*(3)H), 146.0 (C(O)thienyl*C*(2)), 174.6 (*C*O_2H), 182.3 (pyrrolyl(2)*C*(3)); HRMS (NSI$^-$), $C_{14}H_{12}NO_3S$ $[M-H]^-$, requires 274.0543, found 274.0536 (−2.7 ppm).

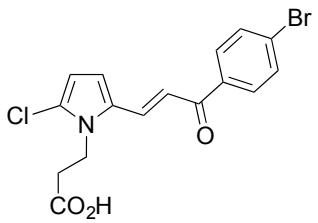
(*E*)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propanoic acid



593

Following general procedure U, pyrrolyl enone ester **592** (1.90 g, 5.63 mmol) and LiOH (709 mg, 16.9 mmol) in H_2O/ethanol (21 mL:21 mL) gave the title compound as a crude residue of 80% purity; ^{1}H NMR (400 MHz, d^6-DMSO) 1.74-1.77 (2H, m, indolyl(6)H_2), 1.81-1.87 (2H, m, indolyl(5)H_2), 2.50-2.53 (2H, m, indolyl(4)H_2), 2.59-2.62 (2H, m, indolyl(7)H_2), 2.70 (2H, t, *J* 6.8, C(2)H_2), 4.26 (2H, t, *J* 6.8, C(3)H_2), 6.69 (1H, s, indolyl(3)*H*), 7.23 (1H, d, *J* 14.9, indolyl(2)C(2)*H*), 7.44-7.54 (3H, m, C(O)Ar(3,5)*H* and C(O)Ar(4)*H*), 7.79 (1H, d, *J* 14.9, indolyl(2)C(1)*H*), 7.98-8.00 (2H, m, C(O)Ar(2,6)*H*). The crude residue was carried forward immediately into the next step without further characterisation.

(*E*)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-5-chloro-1*H*-pyrrol-1-yl)propanoic acid

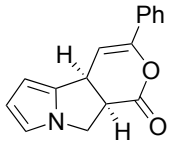


573

Following general procedure U, pyrrolyl enone ester **572** (496 mg, 1.24 mmol) and LiOH (156 mg, 3.72 mmol) in H_2O/ethanol (4.6 mL:4.6 mL) gave the title compound as a brown solid (327 mg, 69%); mp 160-162 °C; ν_{max} (ATR)/cm^{-1} 1558, 1575, 1641 (C=O), 1741 (C=O), 3086 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 2.79 (2H, t, *J* 6.9, C(2)H_2), 4.46 (2H, t, *J* 6.9, C(3)H_2), 6.23 (1H, d, *J* 4.2, pyrrolyl(4)*H*), 6.87 (1H, d, *J* 4.1, pyrrolyl(3)*H*), 7.28 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.63 (2H, d, *J* 8.5, C(O)Ar(3,5)*H*), 7.85-7.90 (3H, m, pyrrolyl(2)C(1)*H* and C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 34.8 (*C*(2)H_2), 39.5 (*C*(3)H_2), 109.8 (pyrrolyl*C*(4)H), 112.8 (pyrrolyl*C*(3)H), 116.3 (pyrrolyl(2)*C*(2)H), 122.5 (C(O)Ar*C*(4)), 128.0 (C(O)Ar*C*(1)), 129.4 (), 130.0 (C(O)Ar*C*(3,5)H), 132.0 (C(O)Ar*C*(2,6)H), 132.7 (pyrrolyl(2)*C*(1)H), 137.2 (pyrrolyl*C*(5)), 173.1 (*C*O_2H), 188.9 (pyrrolyl(2)*C*(3)O); HRMS (NSI$^-$), $C_{16}H_{12}Br^{79}Cl^{35}NO_3$ [M−H]$^-$, requires 379.9694, found 379.9695 (0.25 ppm).

9.6.6 Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation

(4a*S*,9a*R*)-3-Phenyl-4a,9a-dihydro-1*H*,9*H*-pyrano[4,3-*a*]pyrrolizin-1-one

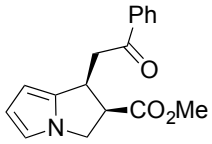


556

Pyrrolyl enone-acid **555** (50.0 mg, 0.19 mmol), *i*-Pr_2NEt (97 μL, 0.56 mmol), pivaloyl chloride (69 μL, 0.56 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (4.7 mg, 0.019 mmol) and *i*-Pr_2NEt (49 μL, 0.28 mmol) gave crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol ether 10:90) afforded the title compound (>95:5 dr) as a yellow oil (39 mg, 84%); $[\alpha]_D^{20}$ +52.2 (*c* 0.5 $CHCl_3$); Chiral HPLC analysis; ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{-1}, 270 nm, 30 °C) t_R 14.3 (major) and t_R 16.4 (minor), >99% ee; ν_{max} (ATR)/cm^{-1} 3028 (C-H), 1728 (C=O), ^{1}H NMR (500 MHz, $CDCl_3$) 3.91 (1H, td, *J* 8.0, 5.0, C(9a)*H*), 4.27 (1H, dd, *J* 4.6, 4.3, C(4a)*H*), 4.37 (1H, dd, *J* 10.8, 8.0, C(9)*Ha*), 4.55 (1H, dd, *J* 10.8, 5.0, C(9)*Hb*), 5.90 (1H, d, *J* 4.6, C(4)*H*), 5.95 (1H, dt, *J* 3.3, 1.1, C(5)*H*), 6.27 (1H, t, *J* 3.1, C(6)*H*), 6.67 (1H, dd, *J* 2.8, 1.1, C(7)*H*), 7.36-7.42 (3H, m, C(3)ArC(3,5)*H* and C(3)ArC(4)*H*), 7.63-7.66 (2H, m, C(3)ArC(2,6)*H*); ^{13}C NMR (126 MHz, $CDCl_3$) 35.8 (*C*(4a)H), 45.2 (*C*(9a)H), 49.0 (*C*(9)H^{a}H^b), 99.6 (*C*(4)H), 100.0 (*C*(5)H), 113.8 (*C*(6)H), 115.2 (*C*(7)H), 125.2 (C(3)Ar*C*(2,6)H), 128.9 (C(3)Ar*C*(4), 129.7 (C(3)Ar*C*(3,5)H), 132.4 (*C*(4b)), 136.6 (C(3)Ar*C*(1)), 148.7 (*C*(3)), 168.3 (*C*(1)); HRMS (NSI$^+$), $C_{16}H_{13}NO_2Na$ $[M+Na]^+$, requires 274.0838, found 274.0843 (+1.8 ppm).

9.6.7 Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation/Ring Opening

Methyl (1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate

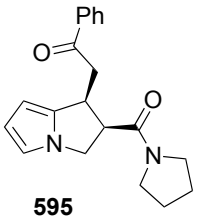


594

Following general procedure V, pyrrolyl enone-acid **555** (50 mg, 0.19 mmol), *i*-Pr_2NEt (97 μL, 0.56 mmol), pivaloyl chloride (69 μL, 0.56 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (2.4 mg, 0.0095 mmol) and *i*-Pr_2NEt (49 μL, 0.28 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a yellow oil (45 mg, 86%); $[\alpha]_D^{20}$ –54.3 (*c* 1.0 in $CHCl_3$); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{-1}, 220 nm), t_R 10.6 (minor) and t_R 12.2 (major), >99% ee; ν_{max} (ATR)/cm^{-1} 2953 (C-H), 1730 (C=O), 1684 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) 3.19-

3.34 (2H, m, pyrrolizine(1)C*H*^{a}H^{b} and pyrrolizine(1)CH^{a}*H*^{b}), 3.58 (3H, s, CO_2CH_3), 4.00 (1H, dd, *J* 16.2, 7.6, pyrrolizine(2)*H*), 4.15 (1H, dd, *J* 11.7, 7.6, pyrrolizine(3)*H*^{a}H^{b}), 4.19-4.26 (1H, m, pyrrolizine(1)*H*), 4.33 (1H, dd, *J* 11.4, 7.2, pyrrolizine(3)H^{a}*H*^{b}), 5.80-5.82 (1H, dt, *J* 3.4, 1.0, pyrrolizine(7)*H*), 6.18-6.22 (1H, m, pyrrolizine(6)*H*), 6.61 (1H, dd, *J* 2.6, 1.2, pyrrolizine(5)*H*), 7.43-7.49 (2H, m, C(O)ArC(3,5)*H*), 7.53-7.58 (1H, m, C(O)ArC(4)*H*), 7.94-7.90 (2H, m, C(O)ArC(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 35.3 (pyrrolizine*C*(1)H), 39.8 (pyrrolizine(1)*C*H^{a}H^{b}), 47.5 (pyrrolizine*C*(3)H^{a}H^{b}), 49.6 (pyrrolizine*C*(2)H), 51.8 (CO_2CH_3), 99.7 (pyrrolizine*C*(7)H), 112.3 (pyrrolizine*C*(6)H), 113.9 (pyrrolizine*C*(5)H), 127.8 (C(O)Ar*C*(2,6)H), 128.5 (C(O)Ar*C*(3,5)H), 133.1 (C(O)Ar*C*(4)H), 136.7 (pyrrolizine*C*(7a)), 137.6 (C(O)Ar*C*(1)), 172.1 (*C*O_2Me), 197.7 (*C*(O)Ar); HRMS (NSI^{+}), $C_{17}H_{18}NO_3$ $[M+H]^{+}$, requires 284.1281, found 284.1284 (+1.1 ppm).

1-Phenyl-2-((1*S*,2*R*)-2-(pyrrolidine-1-carbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)ethan-1-one

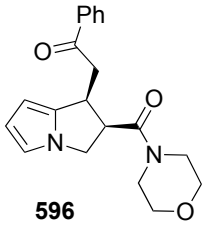


595

Following general procedure V, pyrrolyl enone-acid **555** (100 mg, 0.37 mmol), *i*-Pr_2NEt (195 μL, 1.12 mmol), pivaloyl chloride (138 μL, 1.12 mmol) in CH_2Cl_2 (3.7 mL), (+)-BTM **48** (4 mg, 0.019 mmol), *i*-Pr_2NEt (65 μL, 0.37 mmol) and pyrrolidine (126 μL, 1.51 mmol) gave, after purification by column chromatography (EtOAc:petrol 15:85) to afford the title compound as a yellow oil (119 mg, quant.,); $[\alpha]_D^{20}$ –83.0 (*c* 1.0 in $CHCl_3$); Chiral HPLC analysis ChiralPak IB (90:10 hexane:IPA, 1.0 mlmin^{-1}, 211 nm), t_R 13.0 (major) and t_R 15.6 (minor), >99% ee; ν_{max} (ATR)/cm^{-1} 1610 (C=O), 1682 (C=O), 2951 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 1.75 (2H, p, *J* 7.0, C(O)NC(3)H_2), 1.90-2.04 (2H, m, C(O)NC(4)H_2), 2.97-3.04 (2H, m, ArC(O)C*H*^{a} and C(O)NC(2)*H*^{a}), 3.29-3.36 (1H, m, C(O)NC(2)*H*^{b}), 3.46-3.52 (1H, m, C(O)NC(5)*H*^{a}), 3.56 (1H, dd, *J* 9.8, 8.6, ArC(O)C*H*^{b}), 3.69-3.74 (1H, m, C(O)NC(5)*H*^{b}), 4.01-4.10 (2H, m, C(1)*H* and C(3)*H*^{a}), 4.24-4.29 (1H, m, C(2)*H*), 4.49-4.56 (1H, m, C(3)*H*^{b}), 5.80-5.82 (1H, m, C(7)*H*), 6.21 (1H, t, *J* 3.0, C(6)*H*), 6.62 (1H, dd, *J* 2.7, 1.3, C(5)*H*), 7.41-7.45 (2H, m, C(O)ArC(3,5)*H*), 7.51-7.55 (1H, m, C(O)ArC(4)*H*), 7.89-7.91 (2H, m, C(O)ArC(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 24.3 (C(O)N*C*(3)H_2), 26.1 (C(O)N*C*(4)H_2), 34.2 (*C*(2)H), 40.6 (ArC(O)*C*H^{a}H^{b}), 46.0 (C(O)N*C*(2)H^{a}H^{b}), 46.7 (C(O)N*C*(5)H^{a}H^{b}), 48.2 (*C*(3)H^{a}H^{b}), 49.4 (*C*(1)H), 99.3 (*C*(7)H), 112.4 (*C*(6)H), 114.1 (*C*(5)H), 128.2 (C(O)Ar*C*(2,6)H), 128.7 (C(O)Ar*C*(3,5)H), 133.2 (C(O)Ar*C*(4)H), 136.9 (*C*(7a)), 138.6 (C(O)Ar*C*(1)), 168.6 (*C*O_2NR), 198.3 (*C*(O)Ar); HRMS

(NSI$^+$), $C_{20}H_{23}N_2O_2$ [M+H]$^+$, requires 323.1754, found 323.1754 (+0.0 ppm).

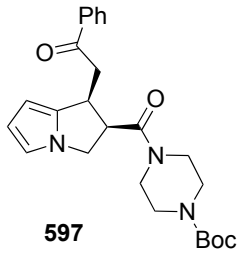
2-((1*S*,2*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)-1-phenylethan-1-one



596

Following general procedure V, pyrrolyl enone-acid **555** (150 mg, 0.56 mmol), *i*-Pr_2NEt (293 μL, 1.68 mmol), pivaloyl chloride (207 μL, 1.68 mmol) in CH_2Cl_2 (5.6 mL), (+)-BTM **48** (7 mg, 0.028 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (>95:5 dr) as a brown oil (29 mg, 66%); $[\alpha]_D^{20}$ –26.2 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak IA (80:20 hexane:IPA, 1.0 mlmin^{-1}, 220 nm), t_R 13.3 (major) and t_R 16.6 (minor), >99:1 er; ν_{max} (ATR)/cm^{-1} 1633 (C=O), 1681 (C=O), 2974, 3064 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.04 (1H, dd, *J* 4.8, 18.1, pyrrolizine(2)*H*), 3.32-3.39 (1H, dd, *J* 6.8, 10.3, pyrrolizine(1)C*H*^{a}H^b), 3.41-3.48 (3H, m, pyrrolizine(1)CH^a*H*^{b} and 2×C(O)NC*H*^{a}H^b), 3.55-3.59 (2H, m, 2×C(O)NCH^a*H*^{b}), 3.63-3.73 (2H, 2×C(O)CH$_2$C*H*^{a}H^{b}O), 3.79-3.82 (1H, m, pyrrolizine(1)*H*), 4.07 (1H, dd, *J* 7.4, 10.1, pyrrolizine(3)*H*^{a}H^b), 4.13-4.19 (2H, m, 2×C(O)CH$_2$CH^a*H*^{b}O), 4.52-4.55 (1H, m, pyrrolizine(3)H^a*H*^{b}), 5.80 (1H, d, *J* 2.8, pyrrolizine(7)*H*), 6.20 (1H, t, *J* 2.8, pyrrolizine(6)*H*), 6.61 (1H, br. s, pyrrolizine(5)*H*), 7.42-7.45 (2H, m, C(O)Ar(3,5)*H*), 7.53-7.56 (1H, m, C(O)Ar(4)*H*), 7.91 (2H, d, *J* 7.5, C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 34.9 (pyrrolizine*C*(1)H), 40.3 (pyrrolizine(1)*C*H^{a}H^{b}COAr), 42.1 (pyrrolizine*C*(2)H), 46.2 (C(O)N*C*^{a}H$_2$), 47.2 (C(O)N*C*^{b}H$_2$), 48.4 (pyrrolizine*C*(3)H^{a}H^b), 66.4 (C(O)NCH$_2$*C*^{a}H$_2$O), 66.6 (C(O)NCH$_2$*C*^{b}H$_2$O), 99.5 (pyrrolizine*C*(7)H), 112.4 (pyrrolizine*C*(6)H), 114.2 (pyrrolizine*C*(5)H), 128.2 (C(O)Ar*C*(2,6)H), 128.7 (C(O)Ar*C*(3,5)H), 133.4 (C(O)Ar*C*(4)H), 136.7 (pyrrolizine*C*(8)), 138.2 (C(O)Ar*C*(1)), 169.0 (*C*(O)NR), 198.0 (*C*(O)Ar); HRMS (NSI$^+$), $C_{20}H_{22}N_2O_3Na$ [M+H]$^+$, requires 361.1523, found 361.1522 (−0.2 ppm).

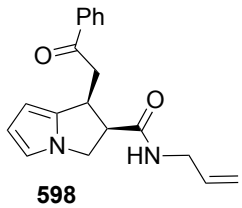
***Tert*-butyl 4-((1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carbonyl)piperazine-1-carboxylate**



597

Following general procedure V, pyrrolyl enone-acid **555** (100 mg, 0.37 mmol), *i*-Pr_2NEt (193 μL, 1.11 mmol), pivaloyl chloride (137 μL, 1.11 mmol) in CH_2Cl_2 (3 mL), (+)-BTM **48** (4 mg, 0.019 mmol), *i*-Pr_2NEt (293 μL, 1.68 mmol) and *N*-Boc piperazine (276 mg, 1.48 mmol) gave, after purification by column chromatography (EtOAc:petrol 20:80) the title compound (>95:5 dr) as a brown oil (121 mg, 75%); $[\alpha]_D^{20}$ –31.6 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 $mlmin^{-1}$, 211 nm), t_R 23.0 (major) and t_R 30.3 (minor), >99:1 er; ν_{max} (ATR)/cm^{-1} 1163, 1633 (C=O), 1681 (C=O), 2927, 2974 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (9H, s, C(C*H*$_3$)$_3$), 2.99-3.06 (1H, m, pyrrolizine(2)*H*), 3.25-3.31 (3H, m, pyrrolizine(1)C*H*^{a}H^{b}COAr and BocNC*H*$_2$), 3.40-3.70 (6H, m, 2×NC*H*$_2$ and BocNC*H*$_2$), 4.04-4.20 (3H, m, pyrrolizine(3)*H*^{a}H^b and pyrrolizine(1)*H* and pyrrolizine(1)CH^a*H*^{b}COAr), 4.50-4.56 (1H, m, pyrrolizine(3)H^a*H*^{b}); ^{13}C NMR (75 MHz, $CDCl_3$) 28.5 (C(*C*H$_3$)$_3$), 35.0 (pyrrolizine*C*(1)H), 40.4 (pyrrolizine*C*(2)H), 41.6 (N*C*H$_2$), 45.7 (BocN*C*H$_2$), 47.5 (pyrrolizine(1)*C*H^{a}H^{b}COAr), 48.4 (pyrrolizine*C*(3)H$_2$), 80.4 (*C*(CH$_3$)$_3$), 99.5 (pyrrolizine*C*(7)H), 112.4 (pyrrolizine*C*(6)H), 114.3 (pyrrolizine*C*(5)H), 128.2 (C(O)Ar*C*(2,6)H), 128.2 (C(O)Ar*C*(3,5)H), 133.4 (C(O)Ar*C*(4)H), 136.8 (pyrrolizine*C*(7a)), 138.2 (C(O)Ar*C*(1)), 154.6 (N*C*(O)C(CH$_3$)$_3$), 168.9 (*C*O$_2$Me), 198.1 (*C*(O)Ar); HRMS (NSI$^+$), $C_{25}H_{32}N_3O_4$ $[M+CH_2+H]^+$, requires 438.2387, found 438.2394 (1.5 ppm).

(1*S*,2*R*)-*N*-Allyl-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxamide

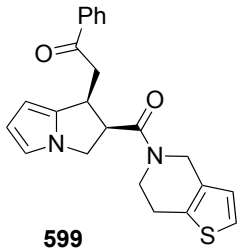


598

Following general procedure V, pyrrolyl enone-acid **555** (150 mg, 0.56 mmol), *i*-Pr_2NEt (293 μL, 1.68 mmol), pivaloyl chloride (207 μL, 1.68 mmol) in CH_2Cl_2 (5.6 mL), (+)-BTM **48** (7 mg, 0.028 mmol), *i*-Pr_2NEt (293 μL, 1.68 mmol) and allyl amine (168 μL, 2.24 mmol) gave, after purification by column chromatography (EtOAc:petrol 15:85) the title compound (>95:5 dr) as

a brown oil (140 mg, 81%); $[\alpha]_D^{20}$ –41.0 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak AD-H (80:20 hexane:IPA, 1.0 mlmin^{-1}, 254 nm), t_R 9.1 (minor) and t_R 11.7 (major), 98.5:1.5 er; ν_{max} (ATR)/cm^{-1} 1637(C=O), 1683 (C=O), 3290 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.33 (1H, dd, *J* 5.3, pyrrolizine(1)C*H*^{a}H^{b}COAr), 3.42 (1H, dd, *J* 8.6, 18.5, pyrrolizine(1)CH^a*H*^{b}COAr), 3.59-3.64 (1H, m, C(O)NHC*H*^{a}H^b), 3.72-3.80 (2H, m, pyrrolizine(2)*H* and C(O)NHCH^a*H*^{b}), 4.09-4.18 (2H, m, pyrrolizine(3)*H*^{a}H^b and pyrrolizine(1)*H*), 4.37 (1H, dd, *J* 6.0, 10.6, pyrrolizine(3)H^a*H*^{b}), 4.96-5.06 (2H, m, =C*H*^{a}H^b and =CH^a*H*^{b}), 5.61 (1H, ddt, *J* 6.0, 10.2, 16.3, C*H*=CH_2), 5.79-5.80 (2H, m, pyrrolizine(7)*H* and C(O)N*H*R), 6.20 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.61 (1H, br. s, pyrrolizine(5)*H*), 7.44-7.47 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.58 (1H, m, C(O)Ar(4)*H*), 7.93-7.94 (2H, m, C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 35.6 (pyrrolizine*C*(1)H), 40.3 (pyrrolizine(1)*C*H^{a}H^{b}C(O)Ar), 42.1 (C(O)NH*C*H^{a}H^b), 48.2 (pyrrolizine*C*(3)H^{a}H^b), 51.4 (pyrrolizine*C*(2)H), 99.4 (pyrrolizine*C*(7)H), 112.6 (pyrrolizine*C*(6)H), 114.1 (pyrrolizine*C*(5)H), 117.1 (=*C*H^{a}H^b), 128.2 (C(O)Ar*C*(2,6)H), 128.7 (C(O)Ar*C*(3,5)H), 133.5 (C(O)Ar*C*(4)H), 133.7 (*C*H=CH_2), 136.7 (pyrrolizine*C*(8)), 138.1 (C(O)Ar*C*(1)), 170.8 (*C*(O)NHR), 199.4 (*C*(O)Ar); HRMS (NSI$^+$), $C_{20}H_{21}N_2O_2$ $[M+H]^+$, requires 321.1598, found 321.1589 (−0.1 ppm).

1-Phenyl-2-((1*S*,2*R*)-2-(4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)ethan-1-one

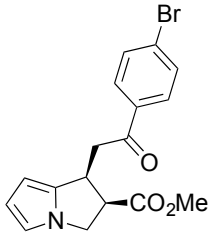


599

Following general procedure V, pyrrolyl enone-acid **555** (100 mg, 0.37 mmol), *i*-Pr_2NEt (193 µL, 1.11 mmol), pivaloyl chloride (137 µL, 1.11 mmol) in CH_2Cl_2 (3 mL), (+)-BTM **48** (4 mg, 0.019 mmol), *i*-Pr_2NEt (293 µL, 1.68 mmol) and 4,5,6,7-tetrahydrothieno[3,2-c] pyridine (260 mg, 1.48 mmol) gave, after purification by column chromatography (EtOAc:petrol 15:85) the title compound (90:10 dr, 50:50 rotameric mixture) as a brown oil (87 mg, 60%); $[\alpha]_D^{20}$ –50.6 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 220 nm), t_R 35.3 (major) and t_R 46.5 (minor), >99:1 er; ν_{max} (ATR)/cm^{-1} 1660 (C=O), 1734 (C=O), 2951, 3089 (C-H); data for single rotamer; ^{1}H NMR (500 MHz, $CDCl_3$) 2.64 (1H, dt, *J* 5.2, 16.0, C*H*), 2.95-2.99 (1H, m, C*H*), 3.03-3.12 (2H, m, 2×C*H*), 3.57 (1H, ddd, *J* 4.7, 7.4, 12.6, C*H*), 3.90 (1H, dt, *J* 5.1, 12.8, C*H*), 4.05-4.13 (4H, m, 4×C*H*), 4.57-4.64 (2H, m, 4×C*H*), 5.83-5.85 (1H, m, pyrrolizine(7)*H*), 6.22 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.64-6.65 (1H, m, pyrrolizine(5)*H*), 6.74 (1H, d, *J* 5.2, thienyl(3)*H*), 7.14 (1H, d, *J* 5.2, thienyl(2)*H*), 7.40-7.44

(2H, m , Ar(3,5)*H*), 7.51-7.56 (1H, m, Ar(4)*H*), 7.82-7.83 (2H, m, Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 24.7 (*C*H), 34.9 (*C*H), 40.2 (*C*H), 43.0 (*C*H), 46.0 (*C*H), 48.1 (*C*H), 48.4 (*C*H), 99.6 (pyrrolizine*C*(7)H), 112.4 (pyrrolizine*C*(6)H), 114.2 (pyrrolizine*C*(5)H), 123.7 (thienyl*C*(2)H), 124.7 (thienyl*C*(3)H), 128.1 (Ar*C*H), 128.7 (Ar*C*H), 132.4 (Ar*C*), 133.3 (Ar*C*), 134.3 (Ar*C*H), 136.7 (Ar*C*), 138.3 (Ar*C*), 169.1 (*C*(O)NR), 197.9 (*C*(O)Ar); HRMS (NSI$^+$), $C_{22}H_{21}N_2O_2S$ $[M+H]^+$, requires 377.1318, found 377.1295 (−6.1 ppm).

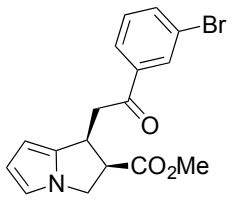
Methyl (1*S*,2*R*)-1-(2-(4-bromophenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



602

Following general procedure V, pyrrolyl enone-acid **561** (60 mg, 0.17 mmol),), *i*-Pr_2NEt (90 μL, 0.52 mmol), pivaloyl chloride (64 μL, 0.52 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (2.2 mg, 0.009 mmol) and *i*-Pr_2NEt (45 μL, 0.24 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a brown solid (49 mg, 78%); mp 120-121 °C; $[\alpha]_D^{20}$ –50.8 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 254 nm), t_R 14.5 (minor) and t_R 17.4 (major), >99% ee; ν_{max} (ATR)/cm^{-1} 1689 (C=O), 1732 (C=O), 2889, 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 3.14-3.30 (2H, m, pyrrolizine(1)C*H*^{a}H^{b}C(O)Ar and pyrrolizine(1)CH^a*H*^{b}C(O)Ar), 3.59 (3H, s, CO_2CH_3), 3.98 (1H, dd, *J* 8.1, 7.8, pyrrolizine(2)*H*), 4.12-4.23 (2H, m, pyrrolizine(3)*H*^{a}H^b and pyrrolizine(1)*H*)), 4.32 (1H, dd, *J* 10.7, 7.4, pyrrolizine(3)H^a*H*^{b}), 5.78-5.81 (1H, m, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.60 (1H, dd, *J* 2.8, 1.2, pyrrolizine(5)*H*), 6.57-6.61 (2H, m, C(O)ArC(3,5)*H*), 7.76-7.81 (2H, m, C(O)ArC(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 35.7 (pyrrolizine*C*(1)H), 40.3 (pyrrolizine(1)*C*H^{a}H^{b}C(O)Ar), 48.0 (pyrrolizine*C*(3)H^{a}H^b), 50.0 (pyrrolizine*C*(2)H), 52.4 (CO_2CH_3), 100.3 (pyrrolizine*C*(7)H), 112.8 (pyrrolizine*C*(6)H), 114.2 (pyrrolizine*C*(5)H), 128.7 (C(O)Ar*C*(4)), 129.9 (C(O)Ar*C*(2,6)H), 132.3 (C(O)Ar*C*(3,5)H), 135.9 (pyrrolizine*C*(7a)), 137.9 (C(O)Ar*C*(1)), 172.47 (*C*O_2Me), 197.2 (*C*(O)Ar); HRMS (NSI$^+$), $C_{17}H_{17}{}^{77}BrNO_4$ $[M+H]^+$, requires 362.0386, found 362.0378 (−2.3 ppm).

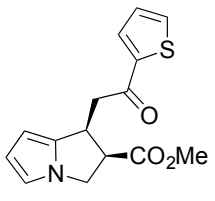
Methyl (1*S*,2*R*)-1-(2-(3-bromophenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



603

Following general procedure V, pyrrolyl enone-acid **562** (100 mg, 0.29 mmol), *i*-Pr_2NEt (151 μL, 0.87 mmol), pivaloyl chloride (107 μL, 0.87 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (4 mg, 0.016 mmol) and *i*-Pr_2NEt (76 μL, 0.44 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a brown oil (84 mg, 80%); $[\alpha]_D^{20}$ –53.4 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 $mlmin^{-1}$, 220 nm), t_R 15.6 (minor) and t_R 17.6 (major), >99% ee; ν_{max} (ATR)/cm^{-1} 1695 (C=O), 1771 (C=O), 2980 (C-H); ^1H NMR (500 MHz, $CDCl_3$) 3.19 (1H, dd, *J* 6.6, 17.8, pyrrolizine(1)C*H*^{a}COAr), 3.28 (1H, dd, *J* 7.6, 17.8, pyrrolizine(1)C*H*^{b}COAr), 3.61 (3H, s, CO_2CH_3), 3.99 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.14-4.21 (2H, m, pyrrolizine(3)*H*^{a} and pyrrolizine(1)*H*), 4.32 (1H, dd, *J* 7.4, 10.6, pyrrolizine(3)*H*^{b}), 5.80 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.61 (1H, dd, *J* 1.2, 2.6, pyrrolizine(5)*H*), 7.33 (1H, t, *J* 7.8, C(O)Ar(5)*H*), 7.68 (1H, ddd, 0.9, 1.8, 7.9, C(O)Ar(4)*H*), 7.83 (1H, dt, *J* 1.1, 7.8, C(O)Ar(6)*H*), 8.04 (1H, t, *J* 1.7, C(O)Ar(2)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 35.4 (pyrrolizine*C*(1)H), 40.2 (pyrrolizine(1)*C*H^{a}H^{b}COAr), 47.8 (pyrrolizine*C*(3)H^{a}H^b), 49.8 (pyrrolizine*C*(2)H), 52.2 (CO_2CH_3), 100.1 (pyrrolizine*C*(7)H), 112.6 (pyrrolizine*C*(6)H), 114.2 (pyrrolizine*C*(5)H), 123.2 (C(O)Ar*C*(3)), 126.6 (C(O)Ar*C*(6)H), 130.4 (C(O)Ar*C*(5)H), 131.2 (C(O)Ar*C*(2)), 136.2 (C(O)Ar*C*(4)H), 137.6 (pyrrolizine*C*(8)), 138.6 (C(O)Ar*C*(1)), 172.2 (CO_2Me), 196.7 (*C*(O)Ar); HRMS (NSI^+), $C_{17}H_{17}Br^{79}NO_3$ $[M+H]^+$, requires 362.0386, found 362.0386 (−0.1 ppm).

Methyl (1*S*,2*R*)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate

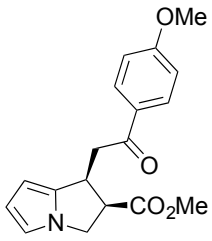


604

Following general procedure V, pyrrolyl enone-acid **566** (100 mg, 0.29 mmol), *i*-Pr_2NEt (151 μL, 0.87 mmol), pivaloyl chloride (107 μL, 0.87 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (4 mg, 0.016 mmol) and *i*-Pr_2NEt (76 μL, 0.44 mmol) gave, after purification by column

chromatography (EtOAc:petrol ether 10:90) the title compound (>95:5 dr) as a brown oil (84 mg, 80%); $[\alpha]_D^{20}$ –75.2 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 270 nm), t_R 18.3 (minor) and t_R 30.9 (major), 99:1 er; ν_{max} (ATR)/cm^{-1} 1661 (C=O), 1724 (C=O), 2895, 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 3.20 (2H, dq, *J* 7.2, 17.2, pyrrolizine(1)C*H*^{a}*H*^{b}), 3.60 (3H, s, CO_2CH_3), 3.97 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.14 (1H, dd, *J* 7.8, 10.7, pyrrolizine(3)*H*^{a}), 4.20 (1H, q, *J* 7.5, pyrrolizine(1)*H*), 4.33 (1H, dd, *J* 7.3, 10.7, pyrrolizine(3)*H*^{b}), 5.80 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.60 (1H, dd, *J* 1.2, 2.6, pyrrolizine(5)*H*), 7.11 (1H, dd, *J* 3.9, 4.9, C(O)thienyl(4)*H*), 7.62-7.65 (2H, m, C(O)thienyl(3)*H* and C(O)thienyl(5)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 35.5 (pyrrolizine*C*(1)H), 40.7 (pyrrolizine(1)*C*H^{a}H^{b}CO), 47.7 (pyrrolizine*C*(3)H^{a}H^b), 49.8 (pyrrolizine*C*(2)H), 52.1 (CO_2CH_3), 100.0 (pyrrolizine*C*(7)H), 112.6 (pyrrolizine*C*(6)H), 114.2 (pyrrolizine*C*(5)H), 128.3 (C(O)thienyl*C*(4)H), 132.1 (C(O)thienyl*C*(3)H), 133.8 (C(O)thienyl*C*(5)H), 137.6 (pyrrolizine*C*(8)), 144.2 (C(O)thienyl*C*(2)), 172.2 (*C*O_2Me), 190.7 (*C*(O)thienyl); HRMS (NSI$^+$), $C_{15}H_{15}NO_3SNa$ $[M+Na]^+$, requires 312.0665, found 312.0660 (−1.6 ppm).

Methyl (1*S*,2*R*)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate

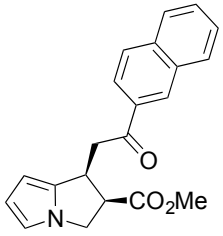


605

Following general procedure V, pyrrolyl enone-acid **560** (42 mg, 0.13 mmol), *i*-Pr_2NEt (70 μL, 0.40 mmol), pivaloyl chloride (50 μL, 0.40 mmol) in CH_2Cl_2 (2 mL), (+)-BTM **48** (1.7 mg, 0.007 mmol) and *i*-Pr_2NEt (35 μL, 0.20 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a yellow oil (41 mg, 98%); %); $[\alpha]_D^{20}$ –61.3 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{-1}, 270 nm) t_R 20.0 (minor) and t_R 25.1 (major) >99:1 er; ν_{max} (ATR)/cm^{-1} 2953 (C-H), 1734 (C=O), 1676 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) 3.12-3.29 (2H, m, pyrrolizine(1)C*H*^{a}H^{b}C(O)Ar and pyrrolizine(1)CH^a*H*^{b}C(O)Ar), 3.57 (3H, s, CO_2CH_3), 3.86 (3H, s, C(O)Ar(4)OCH_3), 3.94-4.02 (1H, m, pyrrolizine(2)*H*), 4.11-4.25 (2H, m, pyrrolizine(3)*H*^{a}H^b and pyrrolizine(1)*H*), 4.33 (1H, dd, *J* 7.1, 10.6, pyrrolizine(3)H^a*H*^{b}), 5.80 (1H, dt, *J* 1.0, 3.4, pyrrolizine(7)*H*), 6.19 (1H, m, pyrrolizine(6)*H*), 6.60 (1H, dd, *J* 1.3, 2.6, pyrrolizine(5)*H*), 6.92 (2H, d, *J* 8.9, C(O)ArC(3,5)*H*), 7.90 (2H, d, *J* 9.0, C(O)ArC(2,6)*H*); ^{13}C

NMR (125 MHz, $CDCl_3$) 35.7 (pyrrolizine*C*(1)H), 39.7 (pyrrolizine(1)*C*H^{a}H^b), 47.8 (pyrrolizine*C*(3)H^{a}H^b), 49.9 (pyrrolizine*C*(2)H), 52.1 (CO_2CH_3), 55.6 (C(O)Ar(4)O*C*H$_3$), 99.9 (pyrrolizine*C*(7)H), 112.5 (pyrrolizine*C*(6)H), 113.8 (C(O)Ar*C*(2,6)H), 114.0 (pyrrolizine*C*(5)H), 130.1 (C(O)Ar*C*(1)), 130.4 (C(O)Ar*C*(3,5)H, 138.0 (C(O)Ar*C*(4)), 163.6 (pyrrolizine*C*(7a)), 172.3 (CO_2Me), 196.4 (*C*(O)Ar); HRMS (NSI$^+$), $C_{18}H_{20}NO_4$ $[M+H]^+$, requires 314.1389, found 314.1388 (+0.3 ppm).

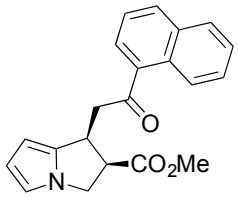
Methyl (1*S*,2*R*)-1-(2-(naphthalen-2-yl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



606

Following general procedure V, pyrrolyl enone-acid **565** (100 mg, 0.31 mmol), *i*-Pr_2NEt (162 µL, 0.93 mmol), pivaloyl chloride (115 µL, 0.93 mmol) in CH_2Cl_2 (3 mL), (+)-BTM **48** (4 mg, 0.016 mmol) and *i*-Pr_2NEt (82 µL, 0.47 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a white solid (84 mg, 81%); mp 108-110 °C; $[\alpha]_D^{20}$ –64.1 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis ChiralPak OD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{-1}, 220 nm, 30 °C), t_R 19.3 (minor) and t_R 26.5 (major), >99:1 er; ν_{max} (ATR)/cm^{-1} 1674 (C=O), 1720 (C=O), 3021 (C-H) ; ^{1}H NMR (400 MHz, $CDCl_3$) 3.35 (1H, dd, *J* 7.8, 17.6, pyrrolizine(1)C*H*^{a}H^{b}C(O)Ar), 3.46 (1H, dd, *J* 7.8, 17.6, pyrrolizine(1)CH^a*H*^{b}C(O)Ar), 3.58 (3H, s, CO_2CH_3), 4.03 (1H, q, *J* pyrrolizine(2)*H*), 4.18 (1H, dd, *J* 7.8, 10.5, pyrrolizine(3)*H*^{a}H^b), 4.29 (1H, q, *J* 7.3, pyrrolizine(1)*H*), 4.37 (1H, dd, *J* 7.2, 10.5, pyrrolizine(3)H^a*H*^{b}), 5.85 (1H, br. s, pyrrolizine(7)*H*), 6.21 (1H, br. s, pyrrolizine(6)*H*), 6.63 (1H, br. s, pyrrolizine(5)*H*), 7.54-7.62 (2H, m, Ar*H*), 7.86-8.03 (4H, m, Ar*H*), 8.42 (1H, br. s, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 35.7 (pyrrolizine*C*(1)H), 40.2 (pyrrolizine(2)*C*H^{a}H^{b}C(O)Ar), 47.8 (pyrrolizine*C*(3)H^{a}H^b), 49.9 (pyrrolizine*C*(2)H), 51.8 (CO_2CH_3), 100.0 (pyrrolizine*C*(7)H), 112.6 (pyrrolizine*C*(6)H), 114.1 (pyrrolizine*C*(5)H), 123.8 (Ar*C*H), 127.0 (Ar*C*H), 127.9 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 129.7 (Ar*C*H), 129.8 (Ar*C*H), 132.6 (Ar*C*), 134.2 (Ar*C*), 135.8 (pyrrolizine*C*(7a)), 137.9 (C(O)Ar*C*(1)), 172.4 (*C*O_2Me), 197.9 (*C*(O)Ar); HRMS (NSI$^+$), $C_{21}H_{19}NO_3Na$ $[M+Na]^+$, requires 356.1257, found 356.1250 (−1.1 ppm).

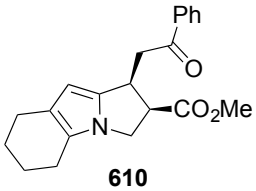
Methyl (1*S*,2*R*)-1-(2-(naphthalen-1-yl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



607

Following general procedure V, pyrrolyl enone-acid **566** (100 mg, 0.31 mmol), *i*-Pr_2NEt (162 μL, 0.93 mmol), pivaloyl chloride (115 μL, 0.93 mmol) in CH_2Cl_2 (3 mL), (+)-BTM **48** (4 mg, 0.016 mmol) and *i*-Pr_2NEt (82 μL, 0.47 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a white solid (74 mg, 72%); $[\alpha]_D^{20}$ –55.2 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{-1}, 211 nm, 30 °C), t_R 12.5 (minor) and t_R 14.2 (major), >99:1 er; ν_{max} (ATR)/cm^{-1} 1165, 1670 (C=O), 1732 (C=O), 2951 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 3.36 (2H, d, *J* 7.2, pyrrolizine(1)C*H*^{a}H^{b}C(O)Ar and pyrrolizine(1)CH^a*H*^{b}C(O)Ar), 3.57 (3H, s, CO_2CH_3), 4.05 (1H, q, *J* pyrrolizine(2)*H*), 4.18 (1H, dd, *J* 7.8, 10.6, pyrrolizine(3)*H*^{a}H^b), 4.30 (1H, q, *J* 7.5, pyrrolizine(1)*H*), 4.35 (1H, dd, *J* 7.1, 10.6, pyrrolizine(3)H^a*H*^{b}), 5.86 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.20 (1H, *J* 3.0, pyrrolizine(6)*H*), 6.62 (1H, dd, *J* 1.2, 2.5, pyrrolizine(5)*H*), 7.46-7.49 (1H, m, Ar*H*), 7.52-7.56 (1H, m, Ar*H*), 7.61 (1H, ddd, *J* 1.3, 6.9, 8.5, Ar*H*), 7.81-7.83 (1H, m, Ar*H*), 7.87-7.88 (1H, m, Ar*H*), 7.98 (1H, br. d, *J* 8.2, Ar*H*), 8.61 (1H, br. d, *J* 8.6, Ar*H*); HRMS (NSI$^+$), $C_{11}H_{12}NO_3$ $[M+H]^+$, requires 206.0823, found 206.0823 (0.0 ppm).

Methyl (1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate

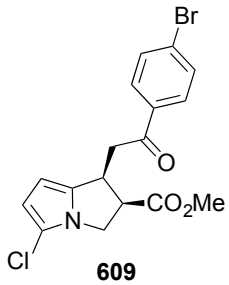


610

Following general procedure V, pyrrolyl enone-acid **593** (100 mg, 0.31 mmol), *i*-Pr_2NEt (162 μL, 0.93 mmol), pivaloyl chloride (115 μL, 0.93 mmol) in CH_2Cl_2 (3 mL), (+)-BTM **48** (4 mg, 0.016 mmol) and *i*-Pr_2NEt (54 μL, 0.31 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (>95:5 dr) as a brown oil (55 mg, 53%); $[\alpha]_D^{20}$ – 33.1 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak IC (90:10 hexane:IPA, 1.0 mlmin^{-1}, 211 nm), t_R 14.7 (major) and t_R 17.4 (minor), >99% ee; ν_{max} (ATR)/cm^{-1} 1665 (C=O), 1730 (C=O), 2841, 2927, 2953 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 1.68-1.74 (2H, m,

pyrroloindolyl(7)H_2), 1.76-1.84 (2H, m, pyrroloindolyl(6)H_2), 2.47-2.55 (4H, m, pyrroloindolyl(8)H_2 and pyrroloindolyl(5)H_2), 3.18 (1H, dd, *J* 6.5, 17.8, pyrroloindolyl(1)CH^aH^{b}COAr), 3.57 (3H, s, CO_2CH_3), 3.92-4.01 (2H, m, pyrroloindolyl(2)*H* and pyrroloindolyl(3)H^a), 4.14 (1H, dd, *J* 7.0, 9.9, pyrroloindolyl(3)H^b), 4.19 (1H, q, *J* 7.4, pyrroloindolyl(1)*H*), 5.59 (1H, s, pyrroloindolyl(9)*H*), 7.43-7.46 (2H, m, C(O)Ar(3,5)*H*), 7.53-7.57 (1H, m, C(O)Ar(4)*H*), 7.91-7.93 (C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 21.9 (pyrroloindolyl*C*(9)H_2), 23.4 (pyrroloindolyl*C*(8)H_2), 23.7 (pyrroloindolyl*C*(5)H_2), 23.8 (pyrroloindolyl*C*(6)H_2), 35.6 (pyrroloindolyl*C*(1)H), 40.5 (pyrroloindolyl(1)*C*H^{a}H^{b}COAr), 45.4 (pyrroloindolylC(3)H^{a}H^b), 49.6 (pyrroloindolyl*C*(2)H), 52.1 (CO_2CH_3), 98.4 (pyrroloindolyl*C*(9)H), 121.3 (pyrroloindolyl*C*(8a)), 122.9 (pyrroloindolyl*C*(4a)), 128.1 (C(O)Ar*C*(3,5)H), 128.7 (C(O)Ar*C*(2,6)H), 133.3 (C(O)Ar*C*(4)H), 135.5 (pyrroloindolyl*C*(9a)), 137.0 (C(O)Ar*C*(1)), 172.5 (*C*O_2Me), 198.1 (*C*(O)Ar); In our hands this compound proved to be unstable to mass spectrometry analysis.

Methyl (1*S*,2*R*)-1-(2-(4-bromophenyl)-2-oxoethyl)-5-chloro-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



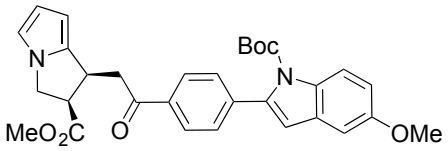
609

Following general procedure V, pyrrolyl enone-acid **573** (40 mg, 0.11 mmol), *i*-Pr_2NEt (55 μL, 0.32 mmol), pivaloyl chloride (39 μL, 0.32 mmol) in CH_2Cl_2 (1 mL), (+)-BTM **48** (1 mg, 0.005 mmol) and *i*-Pr_2NEt (18 μL, 0.11 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (94:6 dr) as a brown oil (29 mg, 66%); $[\alpha]_D^{20}$ –40.1 (*c* 0.5 in $CHCl_3$); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 211 nm), t_R 18.0 (minor) and t_R 21.4 (major), >99:1 er; ν_{max} (ATR)/cm^{-1} 1584 (C=O), 1688 (C=O), 2926, 2951 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 7.1, 17.7, pyrrolizine(1)CH^aH^{b}COAr), 3.24 (1H, dd, *J* 7.2, 17.7, pyrrolizine(1)CH^aH^bCOAr), 3.62 (3H, s, CO_2CH_3), 3.97 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.12 (1H, dd, *J* 7.9, 10.9, pyrrolizine(3)H^aH^b), 4.17-4.27 (2H, m, pyrrolizine(1)*H* and pyrrolizine(3)H^aH^b) 5.74 (1H, dd, *J* 0.8, 3.6, pyrrolizine(7)*H*), 5.97 (1H, d, *J* 3.6, pyrrolizine(6)*H*), 7.60 (2H, d, *J* 8.6, C(O)Ar(3,5)*H*), 7.77 (1H, d, *J* 8.6, C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 36.4 (pyrrolizine*C*(1)H), 39.9 (pyrrolizine(1)*C*H^{a}H^{b}COAr), 46.4 (pyrrolizine*C*(3)H^{a}H^b), 49.3 (pyrrolizine*C*(2)H), 52.3 (CO_2CH_3), 100.9 (pyrrolizine*C*(7)H), 109.6 (pyrrolizine*C*(6)H), 127.5 (C(O)Ar*C*(4)Br), 128.7

(pyrrolizine*C*(8)), 129.6 (C(O)Ar*C*(3,5)H), 132.1 (C(O)Ar*C*(2,6)H), 135.5 (C(O)Ar*C*(1)), 136.4 (pyrrolizine*C*(5)Cl), 171.8 (*C*O_2Me), 196.8 (*C*(O)Ar); HRMS (NSI$^+$), $C_{17}H_{16}Br^{79}ClNO_3$ $[M+Na]^+$, requires 397.9974, found 397.9974 (0.0 ppm).

9.6.8 Derivatisations

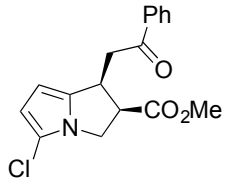
***Tert*-butyl 5-methoxy-2-(4-(2-((1*S*,2*R*)-2-(methoxycarbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)acetyl)phenyl)-1*H*-indole-1-carboxylate**



611

A flame-dried schlenk flask, under inert atmosphere, was charged with $Pd(PPh_3)_4$ (16 mg, 0.014 mmol), pyrrolizine **603** (50 mg, 0.14), Na_2CO_3 (45 mg, 0.42 mmol) and *N*-Boc-5-methoxy-2-indolylboronic acid (49 mg, 0.17 mmol). Degassed DME (2.2 mL) was added and reaction stirred at 80 °C for 16 h. Reaction cooled to rt and dilute with EtOAc, washed with brine (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude reaction mixture that, following column chromatography (EtOAc:Petrol 20:80), gave the title compound (>95:5 dr) as a brown oil (45 mg, 60%); $[\alpha]_D^{20}$ –22.0 (c 0.5 in $CHCl_3$); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 254 nm), t_R 42.6 (major) and t_R 52.0 (minor), >99:1 er; ν_{max} (ATR)/cm^{-1} 1607, 1681 (C=O), 1726 (C=O), 2929, 2951 (C-H); ^{1}H NMR (300 MHz, $CDCl_3$) 1.35 (9H, s, $NCO_2C(CH_3)_3$), 3.20-3.38 (2H, m, pyrrolizine(1)C*H*^{a}H^{b}C(O)indole), 3.62 (3H, s, CO_2CH_3), 3.87 (3H, s, ArOCH_3), 3.97-4.05 (1H, m, pyrrolizine(2)*H*), 4.14-4.27 (2H, m, pyrrolizine(1)*H* and pyrrolizine(3)*H*^{a}H^b), 4.35 (1H, dd, *J* 7.2, 10.6, pyrrolizine(3)H^a*H*^{b}), 5.81 (1H, d, *J* 3.3, pyrrolizine(7)*H*), 6.19-6.21 (1H, m, pyrrolizine(6)*H*), 6.55 (1H, s, indolyl(3)*H*), 6.61 (1H, dd, *J* 1.2, 2.6, pyrrolizine(5)*H*), 6.95-7.03 (2H, m, indolyl(6)*H* and indolyl(7)*H*), 7.50 (2H, d, *J* 8.4, C(O)Ar(3,5)*H*), 7.95 (2H, d, *J* 8.5, C(O)Ar(2,6)*H*), 8.08 (1H, d, *J* 9.0, indolyl(4)*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 27.9 (C(CH_3)$_3$), 35.6 (pyrrolizine*C*(1)H), 40.2 (pyrrolizine(1)*C*H^{a}H^{b}C(O)Ar), 47.8 (pyrrolizine*C*(3)H^{a}H^b), 49.9 (pyrrolizine*C*(2)H), 52.1 (CO_2CH_3), 55.9 (ArOCH_3), 84.0 ($NCO_2C(CH_3)_3$), 100.1 (pyrrolizine*C*(7)H), 103.2 (indolyl*C*(3)H), 111.2 (pyrrolizine*C*(7)H), 112.2 (pyrrolizine*C*(6)H), 113.9 (indolyl*C*(4)H), 114.1 (indolyl*C*(6)H), 116.3 (pyrrolizine*C*(5)H), 127.7 (C(O)Ar*C*(3,5)*H*), 128.9 (C(O)Ar(2,6)*H*), 130.0 (indolyl*C*(2)), 132.6 (indolyl*C*(7a)), 135.8 (indolyl*C*(3a)), 137.9 (pyrrolizine*C*(8)), 139.8 (C(O)Ar*C*(1)), 140.0 (C(O)Ar*C*(4)), 150.1 (N*C*O_2*t*-Bu), 156.3 (indolyl*C*(5)), 172.3 (*C*O_2Me), 197.5 (*C*(O)Ar); HRMS (NSI$^+$), $C_{31}H_{32}N_2O_6Na$ $[M+Na]^+$, requires 551.2158, found 551.2138 (−3.6 ppm).

Methyl (1*S*,2*R*)-5-chloro-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



612

To a solution of pyrrolizine **594** in CH_2Cl_2 (5 mL) at 0 °C, under inert atmosphere was added *N*-chlorosucinimide (47 mg, 0.35 mmol) and reaction stirred for 2 h. Reaction was dilute with CH_2Cl_2 (5 mL), washed with Na_2CO_3 (×3), dried over $MgSO_4$ and concentrated under reduced pressure to give crude reaction mixture that, following column chromatography (EtOAc:Petrol 20:80), gave the title compound (>95:5 dr) as a brown oil (86 mg, 79%); $[\alpha]_D^{20}$ –31.2 (c 0.5 in $CHCl_3$); Chiral HPLC analysis ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin^{-1}, 211 nm), t_R 24.2 (minor) and t_R 39.7 (major), >99:1 er. ν_{max} (ATR)/cm^{-1} 1681 (C=O), 1730 (C=O), 3001 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.18-3.30 (2H, m, pyrrolizine(1)C*H*^{a}H^{b}C(O)Ar and pyrrolizine(1)CH^a*H*^{b}C(O)Ar), 3.61 (3H, s, CO_2CH_3), 3.98 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.12 (1H, dd, *J* 7.8, 10.9, pyrrolizine(3)*H*^{a}H^b), 4.19-4.27 (2H, m, pyrrolizine(3)H^a*H*^{b} and pyrrolizine(1)*H*), 5.75 (1H, d, *J* 3.5, pyrrolizine(7)*H*), 5.97 (1H, d, *J* 3.5, pyrrolizine(6)*H*), 7.44-7.47 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.58 (1H, m, C(O)Ar(4)*H*), 7.90-7.92 (2H, m, C(O)Ar(2,6)*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 36.5 (pyrrolizine*C*(1)H), 39.9 (pyrrolizine*C*(2)H), 46.5 (pyrrolizine(1)*C*H^{a}H^{b}C(O)Ar), 49.3 (pyrrolizine*C*(3)H), 52.2 (CO_2CH_3), 100.9 (pyrrolizine*C*(7)H), 109.5 (pyrrolizine*C*(6)H), 110.1 (), 128.1 (C(O)Ar*C*(3,5)H), 128.8 (C(O)Ar*C*(2,6)H), 133.4 (pyrrolizine*C*(8)). 136.6 (C(O)Ar*C*(1)), 136.8 (pyrrolizine*C*(5)Cl), 171.9 (*C*O$_2$Me), 197.7 (*C*(O)Ar); HRMS (NSI$^+$), $C_{17}H_{17}ClNO_3$ $[M+H]^+$, requires 318.0891, found 318.0893 (+0.6 ppm).

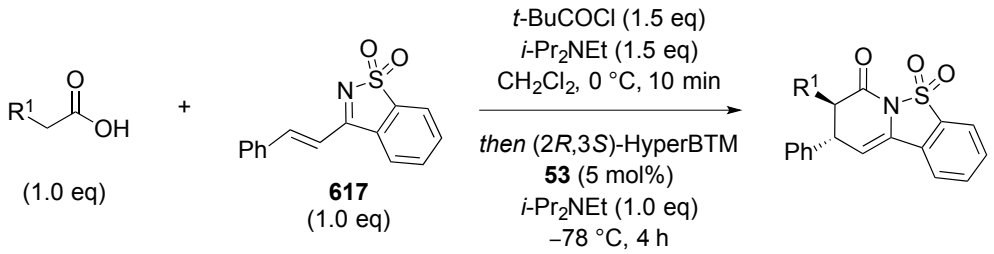
9.6.9 X-Ray Structure Determination

Crystal data for **602**: $C_{17}H_{16}BrNO_3$, M = 362.22, colourless prism, orthorhombic space group *P*21/*c*; *a* = 7.5275(14) Å, *b* = 13.374(3) Å, *c* = 15.278(3) Å, $\alpha = \beta = \gamma = 90°$, *V* = 1538.1(5) Å^3, *Z* = 4, D_c = 1.564 g cm^{-3}, flack parameter = 0.003(1), *R* = 0.0449, R_W = 0.0740 for 2746 data with *I*> 2σ(*I*) and 200 parameters. Data were recorded at 93 K on Rigaku XtaLAB P200 diffractometer using multi-layer mirror monochromated Mo-Kσ radiation and the structures were solved by direct methods and refined using full-matrix least square analysis.

9.7 Experimental for Chapter 7

9.7.1 General Experimental Procedures

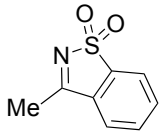
General procedure W: *Isothiourea-Catalysed Michael Addition-Lactamisation*



To a solution of requisite carboxylic acid (1.0 eq) CH_2Cl_2 (0.06 M) were added *i*-Pr_2NEt (1.5 eq) and pivaloyl chloride (1.5 eq) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 10 min then cooled to −78 °C. The requisite Michael acceptor (1.0 eq), (2*R*,3*S*)-HyperBTM **53** (5 mol%), and *i*-Pr_2NEt (1.0 eq) were added and reaction stirred at −78 °C until complete by TLC analysis. The reaction mixture was quenched with aq. HCl (0.1 M) and extracted with CH_2Cl_2 (×3). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude reaction mixture. Products were purified by Biotage® Isolera™ 4 in the solvent system reported.

9.7.2 Preparation of Sulfonyl Imine Substrates

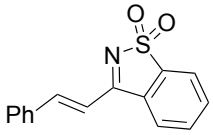
3-Methylbenzo[*d*]isothiazole 1,1-dioxide



633

Following literature procedure,[63] to a solution of saccharin (2.00 g, 10.9 mmol) in THF (109 mL) at 0 °C was added methyl magnesium bromide (3.0 M in Et_2O, 7.27 mL, 21.8 mmol) dropwise. The reaction was warmed to rt and stirred for 16 h before being quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2 (×3). Combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude reaction product. Recrystallisation (CH_2Cl_2) gave the title compound as a white solid (600 mg, 20%); mp 210-212 °C {lit.[196] 213-213.5 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 2.67 (3H, s, C*H*$_3$), 7.73-7.76 (2H, m, Ar(5)*H* and Ar(6)*H*), 7.91-7.93 (1H, m, Ar(4)*H* and Ar(7)*H*). All data in accordance with literature.[196]

(*E*)-3-Styrylbenzo[*d*]isothiazole 1,1-dioxide

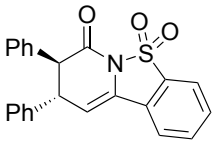


617

Following literature procedure,[156] to a solution of sulfonyl imine **633** (600 mg, 2.23 mmol), in EtOH (7.4 mL) at 80 °C was added benzaldehyde (0.5 mL, 4.91 mmol) followed by piperidine (22 μL, 0.22 mmol), and acetic acid (13 μL, 0.22 mmol). Reaction was stirred at 80 °C for 16 h before being filtered, washed with petrol to give the title compound as a yellow solid (325 mg, 54%); mp 247-248 °C {lit.[197] 245-247 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.31 (1H, d, *J* 15.6, C(3)*H*), 7.48-7.49 (3H, m, Ar*H*), 7.70-7.72 (2H, m, Ar*H*), 7.77-7.78 (2H, m, Ar*H*), 7.89-7.91 (1H, m, Ar*H*), 7.97-7.99 (1H, m, Ar*H*), 8.34 (1H, d, *J* 15.6, C(2)*H*). All data in accordance with literature.[156]

9.7.3 Isothiourea-Catalysed Michael Addition-Lactamisation

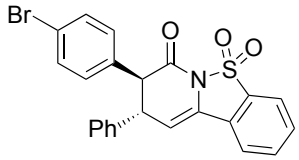
(8*S*,9*S*)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



644

Following general procedure W, phenyl acetic acid (26 mg, 0.19 mmol), pivaloyl chloride (36 μL, 0.29 mmol) and *i*-Pr_2NEt (51 μL, 0.29 mmol) in CH_2Cl_2 (3.2 mL), (2*R*,3*S*)-HyperBTM **53** (3 mg, 0.01 mmol), cyclic sulfonyl imine **617** (50 mg, 0.19 mmol), *i*-Pr_2NEt (33 μL, 0.19 mmol) at −78 °C gave crude reaction mixture (85:15 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (53 mg, 73%) as a white solid (91:9 dr). mp 230-232 °C {Lit.[156] 232-233 °C}; $[\alpha]_D^{20}$ +134.0 (*c* 1.0 $CHCl_3$) {Lit.[156] $[\alpha]_D^{20}$ −177.0 (*c* 1.03 CH_2Cl_2) for 99% ee}; Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R (8*S*,9*S*): 13.1 min, t_R (8*R*,9*R*): 23.0 min; 95% ee; ^{1}H NMR (500 MHz, $CDCl_3$) 4.06 (1H, d, *J* 7.4, C(8)*H*), 4.17 (1H, dd, *J* 4.5, 6.9, C(9)*H*), 6.14 (1H, d, *J* 4.1, C(10)*H*), 7.10-7.17 (4H, m, Ar*H*), 7.26-7.30 (6H, m, Ar*H*), 7.65 (1H, m, Ar*H*), 7.72-7.79 (2H, m, Ar*H*), 7.88-7.92 (1H, m, Ar*H*). All data in accordance with literature.[156]

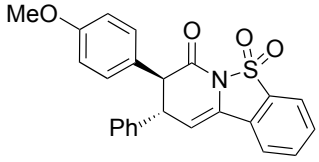
(8*S*,9*S*)-8-(4-Bromophenyl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



645

Following general procedure W, 4-bromophenyl acetic acid (80 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (89:11 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (129 mg, 75%) as a white solid (>95:5 dr). mp 182-184 °C; $[\alpha]_D^{20}$ +78.7 (*c* 0.1 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane:IPA, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R (8*S*,9*S*): 44.6 min, t_R (8*R*,9*R*): 51.5 min; 97% ee; ν_{max} (ATR)/cm^{-1} 1724, 1735, 3028 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 4.00 (1H, d, *J* 9.0, C(8)*H*), 4.17 (1H, dd, *J* 3.8, 9.0, C(9)*H*), 6.12 (1H, d, *J* 3.8, C(10)*H*), 6.99 (2H, d, *J* 8.4, Ar*H*), 7.07 (2H, d, *J* 6.6, Ar*H*), 7.24-7.30 (3H, m, Ar*H*), 7.38 (2H, d, *J* 8.4, Ar*H*), 7.65-7.69 (1H, m, Ar*H*), 7.73-7.75 (2H, m, Ar*H*), 7.89 (1H, d, *J* 7.9, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 47.4 (*C*(9)H), 55.7 (*C*(8)H), 105.9 (*C*(10)H), 121.9 (Ar*C*H), 121.9 (Ar*C*H), 122.0 (C(8)Ar*C*(4)Br), 126.5 (Ar*C*), 127.7 (Ar*C*H), 128.0 (Ar*C*H), 129.3 (Ar*C*H), 129.7 (Ar*C*), 130.5 (Ar*C*H), 131.3 (Ar*C*H), 132.0 (Ar*C*H), 132.8 (Ar*C*), 134.3 (Ar*C*H), 135.0 (*C*(10a)), 140.3 (Ar*C*), 166.0 (*C*(7)); HRMS (NSI^+) $C_{23}H_{16}{}^{79}BrNO_3SNa^+$ $[M+Na]^+$, requires 487.9926, found 487.9913 (−2.8 ppm).

(8*S*,9*S*)-8-(4-Methoxyphenyl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide

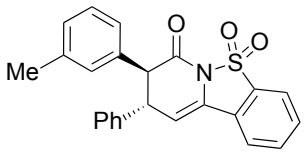


646

Following general procedure W, 4-methoxyphenyl acetic acid (61 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (>95:5 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (129 mg, 75%) as a white solid (>95:5 dr). mp 220-222 °C; $[\alpha]_D^{20}$

+54.4 (*c* 0.1 $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*S*,9*S*): 19.3 min, t_R (8*R*,9*R*): 26.6 min; >99% ee; ν_{max} (ATR)/cm^{-1} 1366, 1724, 1735, 1751, 2970 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.76 (3H, s, ArOC*H*$_3$), 4.01 (1H, d, *J* 7.5, C(8)*H*), 4.13 (1H, dd, *J* 4.4, 7.5, C(9)*H*), 6.13 (1H, d, *J* 4.3, C(10)*H*), 6.79-6.82 (2H, m, C(8)Ar(3,5)*H*), 7.08-7.12 (4H, m, Ar*H*), 7.24-7.31 (3H, m, Ar*H*), 7.66 (1H, ddd, *J* 2.5, 5.9, 8.2, Ar*H*), 7.72-7.76 (2H, m, Ar*H*), 7.90 (1H, d, *J* 7.9, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 47.6 (*C*(9)H), 55.3 (*C*(9)H), 55.4 (ArO*C*H$_3$), 105.7 (*C*(10)H), 114.4 (C(8)Ar*C*(3,5)H), 121.8 (Ar*C*H), 122.0 (Ar*C*H), 126.7 (Ar*C*), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 129.3 (Ar*C*H), 129.6 (Ar*C*H), 129.6 (Ar*C*), 131.2 (Ar*C*H), 132.9 (Ar*C*), 134.2 (*C*(10a)), 140.9 (Ar*C*), 159.2 (C(8)Ar*C*(4)), 166.7 (*C*(7)); HRMS (NSI^+) $C_{24}H_{19}NO_4SNa^+$ $[M+Na]^+$, requires 440.0927, found 440.0924 (−0.7 ppm).

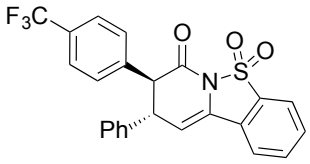
(8*S*,9*S*)-9-Phenyl-8-(*m*-tolyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



647

Following general procedure W, 4-methoxyphenyl acetic acid (56 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (94:6 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (105 mg, 71%) as a white solid (>95:5 dr). mp 174-177 °C {Lit.[156] 177-180 °C}; $[\alpha]_D^{20}$ +166.0 (*c* 1.0 $CHCl_3$) {Lit.[156] $[\alpha]_D^{20}$ −185.0 (*c* 1.03 $CHCl_3$) for 98% ee}; Chiral HPLC analysis, Chiralpak AD-H (70:30 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*S*,9*S*): 14.6 min, t_R (8*R*,9*R*): 27.3 min; >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) 2.11 (3H, s, ArC*H*$_3$), 4.17-4.20 (1H, m, C(9)*H*), 4.29-4.30 (1H, d, *J* 7.1, C(8)*H*), 6.14 (1H, d, *J* 4.1, C(10)*H*), 6.27 (1H, d, *J* 5.2, Ar*H*), 6.45 (1H, br. s, Ar*H*), 6.59 (1H, d, *J* 7.2, Ar*H*), 6.84-6.85 (2H, m, Ar*H*), 6.96-7.03 (2H, m, Ar*H*), 7.15-7.22 (3H, m, Ar*H*), 7.67-7.70 (1H, m, Ar*H*), 7.74-7.80 (2H, m, Ar*H*), 7.92 (1H, d, *J* 7.8, Ar*H*). All data in accordance with literature.[156]

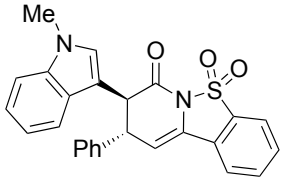
(8*S*,9*S*)-9-Phenyl-8-(4-(trifluoromethyl)phenyl)-8,9-dihydro-7*H* benzo[4,5]isothiazolo [2,3-*a*]pyridin-7-one 5,5-dioxide



648

Following general procedure W, 4-trifluoromethylphenyl acetic acid (76 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (>95:5 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (108 mg, 64%) as a white solid (>95:5 dr). mp 170-172 °C; $[\alpha]_D^{20}$ +59.7 (*c* 0.1 $CHCl_3$); Chiral HPLC analysis, Chiralpak IA (60:40 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*S*,9*S*): 12.0 min, t_R (8*R*,9*R*): 15.9 min; 97% ee; ν_{max} (ATR)/cm^{-1} 1321, 1707, 3158 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 4.13 (1H, d, *J* 9.3, C(8)*H*), 4.19 (1H, dd, *J* 3.7, 9.3, C(9)*H*), 6.16 (1H, d, *J* 3.7, C(10)*H*), 7.08-7.12 (2H, m, Ar*H*), 7.25-7.32 (5H, m, Ar*H*), 7.53 (2H, d, *J* 8.2, Ar*H*), 7.69 (1H, ddd, *J* 2.1, 6.3, 8.1, Ar*H*), 7.76-7.80 (2H, m, Ar*H*), 7.90 (1H, d, *J* 7.9, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 47.4 (*C*(8)H), 56.0 (*C*(9)H), 105.9 (*C*(10)H), 121.9 (Ar*C*H), 121.9 (Ar*C*H), 124.0 (q, *J* 272, *C*F_3), 125.7 (q, *J* 3.6, C(8)Ar*C*(3,5)H), 126.4 (Ar*C*), 127.7 (Ar*C*H), 128.1 (Ar*C*H), 129.3 (Ar*C*H), 129.3 (Ar*C*H), 129.7 (Ar*C*), 130.1 (q, *J* 33.0, C(8)Ar*C*(4)), 131.4 (Ar*C*H), 132.7 (*C*(10a)), 134.4 (Ar*C*H), 140.0 (Ar*C*), 140.1 (Ar*C*), 165.8 (*C*(7)); ^{19}F NMR −62.7; HRMS (NSI$^+$) $C_{24}H_{16}F_3NO_3SNa$ $[M+Na]^+$, requires 478.0695, found 478.0686 (−1.9 ppm).

(8*S*,9*S*)-8-(1-Methyl-1*H*-indol-3-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide

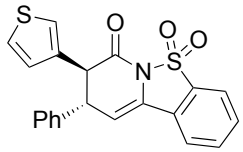


649

Following general procedure W, 1-methyl-3-indoleacetic acid (70 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (80:20 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1

CV)] gave the title compound (97 mg, 60%) as a white solid (89:11 dr). mp 236-238 °C; $[\alpha]_D^{20}$ +69.7 (*c* 1.0 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*S*,9*S*): 12.0 min, t_R (8*R*,9*R*): 15.9 min; >99% ee; ν_{max} (ATR)/cm^{-1} 1333, 1705, 3155 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$) 3.69 (3H, s, NC*H*$_3$), 4.33 (1H, dd, *J* 3.7, 5.6, C(9)*H*), 4.42 (1H, d, *J* 3.7, C(8)*H*), 6.15 (1H, d, *J* 5.6, C(10)*H*), 6.94 (1H, s, indolyl(2)*H*), 7.16-7.20 (1H, m, Ar*H*), 7.25-7.39 (6H, m, Ar*H*), 7.67-7.70 (2H, m, Ar*H*), 7.25-7.28 (2H, m, Ar*H*), 7.92 (1H, d, *J* 7.8, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) 33.0 (N*C*H$_3$), 46.7 (*C*(9)H), 48.0 (*C*(8)H), 105.2 (*C*(10)H), 109.8 (indolyl*C*(7)H), 110.3 (indolyl*C*(3)H), 119.0 (indolyl*C*(4)H), 119.8 (indolyl*C*(5)H), 121.9 (Ar*C*H), 121.9 (Ar*C*H), 122.3 (Ar*C*H), 126.3 (indolyl*C*(2)H), 126.6 (Ar*C*), 126.8 (Ar*C*), 127.4 (Ar*C*H), 128.0 (Ar*C*H), 129.5 (Ar*C*H), 131.1 (Ar*C*H), 132.8 (Ar*C*), 134.2 (Ar*C*H), 137.1 (*C*(10a)), 141.0 (Ar*C*), 166.4 (*C*(7)); HRMS (NSI$^+$) $C_{26}H_{20}N_2O_3SNa$ $[M+Na]^+$, requires 463.1087, found 463.1078 (−1.9 ppm).

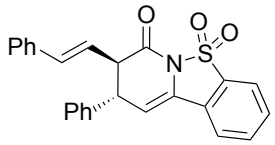
(8*S*,9*S*)-9-Phenyl-8-(thiophen-3-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



650

Following general procedure W, 3-thiopheneacetic acid (53 mg, 0.37 mmol), pivaloyl chloride (69 µL, 0.56 mmol) and *i*-Pr$_2$NEt (98 µL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr$_2$NEt (64 µL, 0.37 mmol) at −78 °C gave crude reaction mixture (93:7 dr). Purification by Biotage® Isolera^{TM} 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (112 mg, 77%) as a white solid (>95:5 dr). mp 198-200 °C; $[\alpha]_D^{20}$ +79.3 (*c* 0.1 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*S*,9*S*): 21.7 min, t_R (8*R*,9*R*): 44.0 min; >99% ee; ν_{max} (ATR)/cm^{-1} 1355, 1709, 3001 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 4.16-4.20 (2H, m, C(8)*H* and C(9)*H*), 6.15 (1H, d, *J* 4.6, C(10)*H*), 7.04-7.08 (2H, m, Ar*H*), 7.16-7.17 (2H, m, Ar*H*)7.27-7.33 (4H, m, Ar*H*), 7.65 (1H, m, Ar*H*), 7.72 (2H, m, Ar*H*), 7.84 (1H, d, *J* 7.8, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 46.8 (*C*(9)H), 51.5 (*C*(8)H), 105.1 (*C*(10)H), 121.9 (Ar*C*H), 121.9 (Ar*C*H), 126.6 (Ar*C*H), 127.0 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 128.0 (Ar*C*H), 129.4 (Ar*C*H), 129.6 (Ar*C*), 131.3 (Ar*C*H), 132.8 (), 134.3 (Ar*C*H), 136.1 (*C*(10a)), 140.4 (Ar*C*), 165.9 (*C*(7)); HRMS (NSI$^+$) $C_{21}H_{16}NO_3S_2$ $[M+H]^+$, requires 394.0572, found 394.0561 (−2.8 ppm).

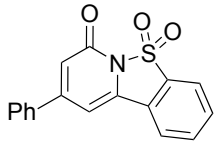
(8*R*,9*S*)-9-Phenyl-8-((*E*)-styryl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



651

Following general procedure W, (*E*)-4-phenylbut-3-enoic acid (60 mg, 0.37 mmol), pivaloyl chloride (69 μL, 0.56 mmol) and *i*-Pr_2NEt (98 μL, 0.56 mmol) in CH_2Cl_2 (6 mL), (2*R*,3*S*)-HyperBTM **53** (5 mg, 0.019 mmol), cyclic sulfonyl imine **617** (100 mg, 0.37 mmol), *i*-Pr_2NEt (64 μL, 0.37 mmol) at −78 °C gave crude reaction mixture (95:5 dr). Purification by Biotage® Isolera™ 4 [SNAP 25 g, 75 mL^{-1}, hexane:EtOAc (97:3 4 CV, 97:3 to 50:50 10 CV, 50:50 1 CV)] gave the title compound (98 mg, 64%) as a white solid (95:5 dr). mp 204-206 °C; $[\alpha]_D^{20}$ +81.1 (*c* 1.0 CH_2Cl_2); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R (8*R*,9*S*): 15.6 min, t_R (8*S*,9*R*): 25.8 min; 71% ee; ν_{max} (ATR)/cm^{-1} 1366, 1728, 1736, 2970 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) 3.66 (1H, t, *J* 6.6, C(8)*H*), 3.96 (1H, t, *J* 5.0, C(8)*H*), 6.10 (1H, d, *J* 4.5, C(8)C(1)*H*), 6.17 (1H, dd, *J* 7.6, 15.9, C(8)C(2)*H*), 6.42 (1H, d, *J* 15.9, C(10)*H*), 7.20-7.34 (10H, m, Ar*H*), 7.61-7.64 (1H, m, Ar*H*), 7.70-7.72 (2H, m, Ar*H*), 7.85 (1H, d, *J* 7.8, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) 45.9 (*C*(9)H), 53.3 (*C*(8)H), 105.0 (C(8)*C*(1)H), 121.9 (Ar*C*H), 121.9 (Ar*C*H), 123.4 (C(8)*C*(2)H), 126.7 (Ar*C*H), 126.7 (Ar*C*H), 127.7 (Ar*C*H), 128.0 (Ar*C*), 128.2 (Ar*C*), 128.7 (Ar*C*H), 129.4 (Ar*C*H), 129.6 (Ar*C*), 131.2 (Ar*C*H), 132.8 (Ar*C*), 134.2 (Ar*C*H), 135.3 (Ar*C*H), 136.3 (*C*(10a)), 140.3 (Ar*C*), 166.2 (*C*(7)); HRMS (NSI^+) $C_{25}H_{20}NO_3S$ $[M+H]^+$, requires 414.1164, found 414.1139 (−6.0 ppm).

9-Phenyl-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide



660

To a solution of acyl imidazole **661** (81 mg, 0.37 mmol) in CH_2Cl_2 was added cyclic sulfonyl imine **617** (100 mg, 0.37 mmol) and DHPB **86** (7 mg, 0.037 mmol) and reaction stirred at rt for 6 h. Reaction was washed with aq. HCl (2 M) (×3), sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure to give crude reaction product. Recrystallisation (Et_2O) gave the title compound as a white solid (100 mg, 88%); mp >300 °C; ν_{max} (ATR)/cm^{-1} 1724, 2895, 2951 (C-H); ^{1}H NMR (500 MHz, d_6-DMSO) 6.91 (1H, s, C(10)*H*), 7.54-7.55 (3H, m, Ar*H*), 7.74 (1H, s, C(8)*H*), 7.83-7.90 (3H, m, Ar*H*), 7.98 (1H, t, *J* 7.6, Ar*H*), 8.26 (1H, d, *J* 7.8, Ar*H*), 8.47 (1H, d, *J* 7.9, Ar*H*); ^{13}C NMR (125 MHz, d_6-DMSO) 107.8 (*C*(8)H), 118.1

(*C*(10)H), 122.3 (Ar*C*H), 123.9 (Ar*C*H), 125.1 (Ar*C*), 127.3 (Ar*C*H), 129.1 (Ar*C*H), 130.7 (Ar*C*H), 131.8 (Ar*C*), 133.0 (Ar*C*H), 135.4 (Ar*C*), 135.5 (Ar*C*H), 135.5 (Ar*C*), 153.2 (Ar*C*), 158.4 (*C*(7)); HRMS (NSI^+) $C_{17}H_{11}NO_3S^+$ $[M+H]^+$, requires 309.0460, found 309.0451 (−1.3 ppm).

9.8 References and Notes

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